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Symposium on Overnutrition

Foreword

THE modern era of nutrition has been marked by the discovery of a host of nutrients required by the body and a corresponding number of deficiency syndromes. The past half century has seen the number of essential nutrients increase from a paltry dozen to approximately forty. It has been an exciting development. The possibilities of preventing disease by diet—not only nutritional disease but other diseases, too—has stirred the imagination, and enthusiasm has grown to make sure that everyone had enough and to spare. The task of meeting nutritional requirements is by no means accomplished. There are large segments of the world, the so-called "technically underdeveloped" countries, where undernutrition is an acute and most pressing problem. In the well developed countries, however, and in the upper economic groups of any population, evidence is accumulating that we may have overshot the mark. Clear-cut deficiency disease is a rarity; what passes for it is often highly questionable.

The life insurance companies were the first to call our attention to the possibilities of overnutrition. Their statistical data revealed that overweight increased the mortality from heart disease and cancer, and underweight decreased the risk of succumbing to these conditions. Caloric overnutrition is now generally recognized as undesirable, but the possibilities of overnutrition with specific nutrients have only recently received attention.

Although definite conclusions in this area must await further work, there is both experimental and suggestive clinical evidence which suggests that we should watch our intake of protein, saturated fat, certain minerals (such as calcium and iron) and some of our vitamins, especially the fat-soluble vitamins. The possibility of remote effects is one that requires serious thought. There is much concern in adult medicine about the

etiology of atherosclerosis, a condition which seems to be definitely related to nutrition and probably to overnutrition, although the exact factors are matters of dispute. It is of interest, therefore, to learn that this disease has its roots in childhood. If it is a nutritional problem, it is therefore a pediatric nutritional problem.

Even though knowledge about overnutrition is in its infancy, it is important for the pediatrician to keep abreast of it. The contributors to this symposium have kindly consented to help us out in this regard.

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Introductory Remarks

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THIS is a unique session as far as nutrition is concerned. During the course of this International Congress, there are to be no fewer than eight separate symposia in this field. This will be the only one specifically devoted to the subject of overnutrition. Most of the others will deal with undernutrition in one form or another.

A word of appreciation is due to Dr. Emmett Holt, who is responsible for the organization of this symposium. It was he who brought together the members of our panel of experts. Perhaps it is significant, and quite proper, that the panel members are all from the United States, which can boast of having one of the best-fed populations in the world.

In this connection, the following quotation from *The Lancet* seems appropriate: "Once upon a time there was a very poor country where nobody had enough to eat, and the average expectation of life was twenty-four years. There was also a very rich country where everybody had plenty to eat, and the average expectation of life was sixty-four years. In the very rich country, people used to save up milk and butter and cream and eggs and send them to the very poor country where they were distributed, especially to the children who would otherwise have had none. In this way the expectation of life in the very poor country was raised from twenty-four to twenty-seven years. Meanwhile, the expectation of life in the very rich country was rising too and went up from sixty-four to sixty-seven years, and everyone who did not die of cancer of the lung from smoking too many cigarettes, died of coronary thrombosis. Then someone discovered that coronary thrombosis was due to eating and drinking too much milk and butter and cream and eggs in the very rich country. So they sent all these materials to the very poor country, so that the expectation of life in the very poor country might be raised high enough for them to start dying of coronary thrombosis so that they, too, could stop eating and drinking milk and butter and cream and eggs."[1]

The relevancy of the subject of overnutrition should be evident to any observer of infants and children in the United States. Significant malnutrition is distinctly uncommon whereas the practitioner has to deal with an increasing number of obese persons. This is not to deny the prevalence of serious malnutrition in many parts of the world; it is rather that the nutritional considerations of other areas should not lead us to overlook the fact that overnutrition is a greater potential problem in this particular part of the world.

A number of years ago, the experiments of McCay and his associates[2] demonstrated that the life span of rats could be lengthened through systemic underfeeding. These findings have been recently confirmed by Ross.[3] Life insurance data[4] indicate that the overweight adult subject has a shortened life expectancy. Although no data are available for children, these observations, and others, indicate the need for attempting to evaluate the potential effects of overnutrition on the child.

There can be no doubt that the child of today grows faster and matures earlier than in previous decades; this phenomenon has occurred in European countries as well as in the United States.[5] A number of factors have undoubtedly contributed to this trend, but prominent among these is the fact that children are now better fed. The progressive increase

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TABLE I
A Contrast in the Nutritional Scene

Data	United States	Underdeveloped Area
Food supply.....	Abundant	Limited
Food quality, especially protein.....	Excellent (high intake of animal protein)	Poor (largely vegetable protein)
Customs and attitudes.....	Primacy of the child; indulgence	Child may be last to eat at family meal; separation common
Concept of disease therapy...	Repletion—"feed a cold"	Exercise evil influence; fasting
Incidence of intercurrent disease.....	Low	High

in height and weight which has occurred in school children of Stuttgart, Germany, between 1910 and 1950, has been interrrupted on only two occasions—World War I and World War II, both periods of decreased food supply. Japanese children reared in this country are larger than their brothers left at home.[6] During the past half-century, American boys have increased in height by 6 to 8 per cent and in weight by 12 to 15 per cent.[7] Furthermore, the average age of menarche has shown a progressive decline over the years, amounting to some three and a half years in Norway during the past century.[5] All these data are offered in support of the premise that the modern child is better fed, for growth and development are both very sensitive indicators of the level of nutritional intake.

What are the factors which tend to promote overnutrition in the United States? First is the decline in chronic disease; for it is well known that disease interferes with nutritional performance and growth. Such diseases as rheumatic fever, chronic osteomyelitis and tuberculosis, to mention just a few, are much less common today.

The advanced technology of food production and distribution is another factor: We produce more food than we can eat, and it is food of high quality made readily available by efficient technics of distribution. Vitamin manufacture, virtually nonexistent prior to 1937, is now being carried out on a truly prodigious scale. For example, in 1955, we produced some 1,200 tons of ascorbic acid[8]—enough to provide every person in this country with 20 mg. daily—in addition to that which naturally occurs in foods. The dollar volume of vitamin manufacture in 1955 amounted to some $83,000,000.

Promotional advertising has as its goal the consumption of increasing amounts of food and food supplements. The public is constantly being urged to eat more and more. One even sees schemes promising that one can "eat and still reduce."

The attitude of the public is an important factor. Although overt obesity is not countenanced in our society, many parents are happier when their children grow at a rapid rate. The concept of "bigness" is as firmly established in the rearing of children as it is in the economic and industrial life of today. Babies are being fed solid foods at an earlier age, vitamin supplements are commonly given in doses which exceed those needed to prevent deficiency states, infant formulas are more concentrated than formerly.

Lastly, the attitudes of the nutritionist and the pediatrician have played an influential role. Nutritional science, and to a certain extent modern pediatrics, owes its origin to the deficiency concept of disease. This is the concept which states that disease can be due to lack of something in the diet. In the realization that optimum requirements are difficult to define, the physician and the nutritionist have sometimes taken the position of recommending that more be offered to the child, so that there will be no question about the adequacy of the intake. Much attention has been given to attempts to uncover "subclinical" malnutritive states; perhaps we should now turn our attention to subclinical overnutriture as well. Is it possible that in our efforts to insure an adequate diet for everyone, we are feeding some children too much?[9] Perhaps it would be well to consider the definition of the

word "optimum" as it applies to nutrition, particularly the nutrition of infants and children.

It is of interest to draw a contrast between the United States and some underdeveloped region, such as one in which the term "kwashiorkor" originated, with respect to some of these factors (Table 1).

Customs and attitudes do play an important role in nutritional performance. In our culture it appears to be of the utmost importance that the child be fed well; in certain primitive societies, the nourishment of the father is paramount. The common practice of sending the toddler away to live with relatives must certainly have some impact on emotional adjustment and appetite performance at this early age. Many primitive mothers follow the custom of reducing food intake at time of illness, and it is common for symptoms of kwashiorkor to appear in association with intercurrent disease.

Obviously, these generalizations do not apply in all instances (not all people in the United States have an adequate diet, and there are well nourished people in India), but they do serve to point out significant differences in cultural and social phenomena. It is evident that the sum total of the various forces in our culture are largely in the direction of overnutrition, while those in some primitive cultures act in the opposite direction. In our society we have operated on the assumption that maximum growth is optimum, an assumption which may or may not be valid for man.

At the dawn of modern pediatrics, there were many forces at work in the direction of undernutrition; today these have been replaced, at least in our part of the world, by forces operating to promote overnutrition. It is the ease with which overnutrition can now be achieved that constitutes such an impetus to its occurrence. Perhaps it is time for a new perspective in infant nutrition.[10]

REFERENCES

1. A running commentary by peripatetic correspondents. *Lancet*, 1: 635, 1956.
2. McCay, C. M., Sperling, G. and Barnes, L. L. Growth, aging, chronic diseases and life span in rats. *Arch. Biochem.*, 2: 469, 1943.
3. Ross, M. H. Protein, calories and life expectancy. *Fed. Proc.*, 18: 1190, 1959.
4. Dublin, L. I. Relation of obesity to longevity. *New England J. Med.*, 248: 971, 1953.
5. Tanner, J. M. Growth at Adolescence. Springfield, Ill., 1955. Charles C Thomas.
6. Gruelich, W. W. Growth of children of the same race under different environmental conditions. *Science*, 127: 515, 1958.
7. Meredith, H. V. Stature and weight of children of the United States. *Am. J. Dis. Child.*, 62: 909, 1941.
8. U. S. Tariff Commission Reports for 1955 (Report No. 198).
9. Forbes, G. B. Overnutrition for the child: Blessing or curse? *Nutrition Rev.*, 15: 193, 1957.
10. Forbes, G. B. Do we need a new perspective in infant nutrition?, *J. Pediat.*, 52: 496, 1958.

Obesity: Physiologic Considerations

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PERHAPS it might be useful, before we speak about what may cause obesity and what may be able to be done about it, to define it and to give the basis for proper diagnosis.

Obesity is the presence of an excessive amount of fat in the organism. I say "fat" and not "weight" because the excessive amount of adipose tissue is what we are concerned with.

The immediate implication in terms of diagnosis is that the way to decide whether or not a child is obese is to determine his actual fat content. In adults, a great deal of emphasis has been placed on the use of height-weight tables. I, for one, think they are inadequate: They only give unequivocal results when the subject is so fat and so overweight that there is not much doubt about his obesity anyway. When the subject contains a moderate proportion of fat, height-weight ratios are difficult to interpret. The fact that the tables give reference to body frame (small, medium, or large) is of little help, as no instruction is given for determining a given subject's frame.

Under office conditions, in children as in adults, the best way to determine whether your patient is fat is to look at him or her. If the patient looks fat, he probably is fat. If you have any doubt about it, you pinch the patient in appropriate places; if the patient feels fat, then that clinches the diagnosis of obesity.

If you want to be scientific about it, you can use constant pressure calipers and, with a minimum amount of practice, you can get fairly reproducible results.

In man, more than half of the total fat of the body is subcutaneous and, therefore, calipers give a good estimate of the over-all amount of fat. This is not a complicated procedure, and I think it has its place not only in scientific studies but also in routine clinical work, in following the evolution of fatness in patients. This is particularly true in children, as their weight is going to increase anyway as they grow; following weight alone is far less informative than following fat content. Therefore, this is a plea for looking at the patient rather than looking at life insurance tables.[1]

Why are we concerned with the problem of obesity? First, because of the implications in terms of health, implications which are familiar to all.[2] At the same time most patients are concerned about obesity from the point of view of appearance, and this motivation is an important point to keep in mind in the therapeutic approach to children as well as to adults.

REGULATION OF FOOD INTAKE

I intend to review briefly what is known about the regulation of food intake. I think this is necessary because the field of obesity is one which has suffered from a tremendous amount of oversimplification. Many health agencies are quite satisfied with the blanket statement that patients are obese because they eat too much.

To me, that statement has always been just about as illuminating as saying that somebody is an alcoholic because he drinks too much. Once you have said the patient eats too much (that is, more than he requires), you really have redefined the problem but not explained it. You first have to find out why it is that he eats

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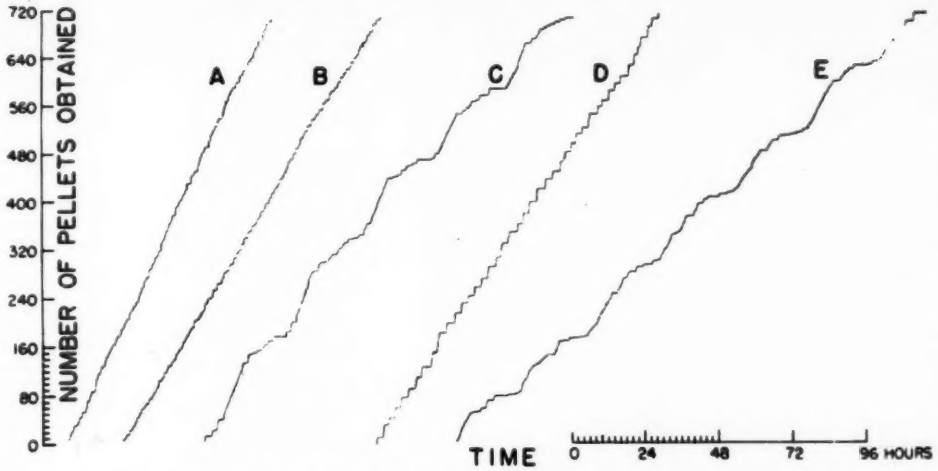

FIG. 1. Cumulative records of pellets of food consumed by mice: Differences in pattern of food intake between normal mice (C and E) and obese mice (A-goldthioglucose hypothalamic; B-hypothalamic where lesions have been made with a stereotaxic instrument; D-obese hyperglycemic). From: MAYER, J. *Metabolism*, 6: 435, 1957.[16]

too much. The fact that we do not have the answer in the great majority of cases is testified to by the extraordinarily poor record of weight reduction programs.

Dr. Trulson,[3] in our department, and Dr. Stunkard[4] have studied groups of obese patients on a number of different treatment regimens. In general, the studies are very much along the same lines. Groups are directed to either nutrition clinics in large hospitals or to group dynamics operations, or they receive individual psychotherapy. They are compared with patients who are left untreated. Although there are some differences between these treated groups and groups of patients left untreated, the results on a long-term basis are universally poor. All this indicates that it is time to look again at the fundamental mechanisms and wonder whether, in effect, we know what we are doing.

The problem of regulation of food intake has been curiously neglected for a long time, at least if you compare it to that of some of the other important regulations in the organism, such as the regulation of blood pH. There are a number of areas in the body which are now known to be quite intimately concerned with this mechanism: (1) the gastrointestinal tract, with the presence of gastric contractions, as first shown by Cannon, and later by Carlson, and (2) various areas of the central nervous system, in particular the hypothalamic and thalamic centers and certain areas in the cortex, particularly the frontal lobes.[5]

Recently, it has become possible to try to integrate in experimental animals these various neural mechanisms with behavioral mechanisms and with metabolic phenomena.

Figure 1 depicts a number of patterns showing how normal animals eat and how treated animals eat. C and E represent normal patterns of intake for mice: a period of satiety is followed by a period of eating. A and B represent the patterns of food intake in animals after the ventromedial area of the hypothalamus has been destroyed. These animals do not eat more rapidly than do normal animals, but the normal satiety patterns has been eliminated.[6] Incidentally, when an animal is exercised or exposed to the cold, we find that the way in which it adjusts its food intake to the increased needs is by varying the length of the satiety pattern rather than the rate of eating. All that is eliminated when the ventromedial area is destroyed.[7] This and additional evidence of a similar nature led us to conclude that the ventromedial area of the

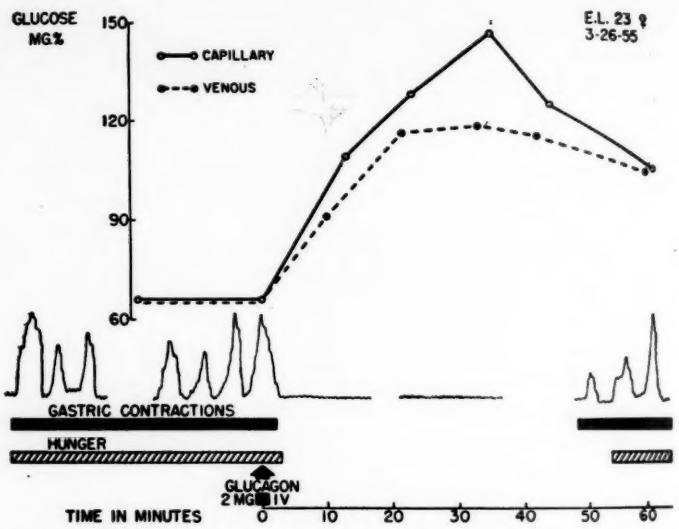

FIG. 2. Besides demonstrating the effects of glucagon this figure illustrates the correlation between greater arteriovenous glucose differences and disappearance of gastric contractions and hunger feelings. It also underlines the fact that the *absolute* blood glucose level shows no such correlation. From: STUNKARD, A. J., VAN ITALLIE, T. B. and REIS, B. B. *Proc. Soc. Exper. Biol & Med.*, 89: 258, 1955.[8]

hypothalamus is essentially concerned with adjusting food intake to energy output; in other words, regulating one as a function of the other.

The analysis can be pushed further by teaching animals to (1) feed themselves through intragastric fistula so as to eliminate taste factors; (2) feed themselves by injecting food intravenously, thus eliminating gastrointestinal factors; and (3) directly stimulate those centers in the hypothalamus which have to do with food intake, so as to deal solely with the nervous factors and bypass the metabolic factors altogether.

The next problem is to try to see how the mechanism works: how is the food intake adjusted to the energy output in the ventromedial area? We have come to the conclusion that this is concerned with carbohydrate metabolism as it takes place within this area of the hypothalamus.

The evidence in favor of this concept is manyfold: (1) There is an excellent correlation between the rate at which carbohydrate is utilized in the body, and the presence or absence of hunger feelings and gastric contractions in both men and animals.[5,8] (2) This area has very special properties in regard to carbohydrate metabolism. For example, it is extraordinarily receptive to goldthioglucose which produces considerable cell destruction and edema localized to the ventromedial area. By contrast, when gold is linked by a sulfur bridge to compounds other than glucose, such as galactose, caprylic acid, caproic acid, glycerol or sorbitol such an effect is not apparent. It has been shown by Larsson,[9] and more recently by Larsson and Chain,[10] and by Anand,[11] that, in regard to carbohydrate metabolism, this area has very different properties from the rest of the brain and even from the rest of the hypothalamus.

One of the aspects of regulation of food intake is the presence of gastric contractions. In Figure 2, which is from an experiment conducted by Stunkard,[12] we see the effect of glucagon on glucose utilization, gastric contractions and hunger in man. As glucose utilization rises, gastric contractions and hunger feelings disappear. They reappear when glucose utilization is again reduced, even

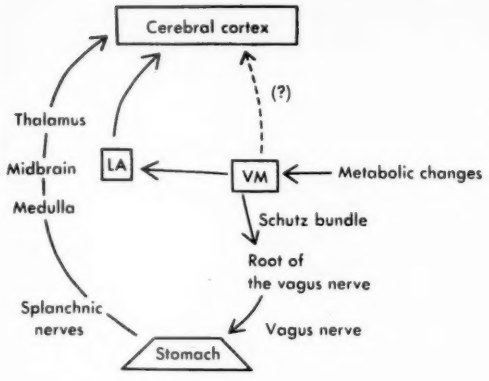

FIG. 3. An integrated view of the mechanism of the regulation of food intake. From: MAYER, J. *Postgraduate Med.*, 25: 624, 1959.

though the blood glucose level is higher than under fasting conditions.

We have shown that the effect on gastric contractions disappear when the ventromedial area is destroyed. In other words, the effect of glucagon on gastric contractions appears to be mediated through the effect of carbohydrate metabolism on the ventromedial area of the hypothalamus.[13] (The effect of epinephrine and of norepinephrine persists after destruction of this hypothalamic area.)

Figure 3 shows our general scheme for the mechanism of regulation of food intake. Metabolic changes act on the ventromedial area; the ventromedial area in turn acts on the lateral hypothalamus, destruction of which causes animals to stop eating altogether. From there on, projections go to the cortex.

At the same time, there is another method of awareness of this "metabolic" hunger, namely, impulses going down from the ventromedial area, probably down the Schutz' bundles to the roots of the vagus, and influencing or controlling gastric contractions. These contractions may also originate in part in the stomach itself. Through impulses carried up by the splanchnic nerves, the organism can thus become conscious of hunger as a gastric phenomenon as well as a central phenomenon.

There are in addition to metabolic factors, a great many other factors which affect food intake: temperature, dehydration and psychologic factors acting at a higher level. These factors may be the dominant factors at a given time and supersede the metabolic state; the latter, however, has a "memory" built into itself and is in the proper sense of the term "regulatory."

The existence of this complicated mechanism (Fig. 4) obviously opens up the possibility of a great many things going wrong with it. Whenever you have a complicated machine, it not only *can* go wrong, it *does* go wrong, and it can go wrong in a great many places.

INCREASE IN FOOD INTAKE

We are all prepared for the idea that *lack of appetite* may be due to many different and unrelated causes: disease, unappetizing food, bad news or a blow on the head. By contrast, most of us are unprepared for the idea that a great many unrelated factors will increase food intake. I have tried to classify these factors according to the classic epidemiologic concepts of host, agent and environment.[14] Host factors or constitutional factors are essentially genetic. There are a number of genetic forms of obesity in experimental animals. We have studied four or five different kinds in the mouse alone. There are at least two obese genes known in the rat, and some known in the dog, the chicken, and so on. In man, while the degree of influence of genetic factors on obesity cannot be quantitatively assessed on the basis of the evidence at hand, there is enough evidence to induce us to stop denying their role.

It is more important and more useful to use the fact that the children of obese parents are much more likely to be obese, not only for environmental reasons but for genetic reasons as well, so as to anticipate trouble. Our preventive efforts should be concentrated on such children because they, in turn, are likely subjects for obesity.

In the sample which we have studied in the Boston area, about 8 or 9 per cent of children of normal weight parents are obese by criteria we have used. If one parent is obese, the

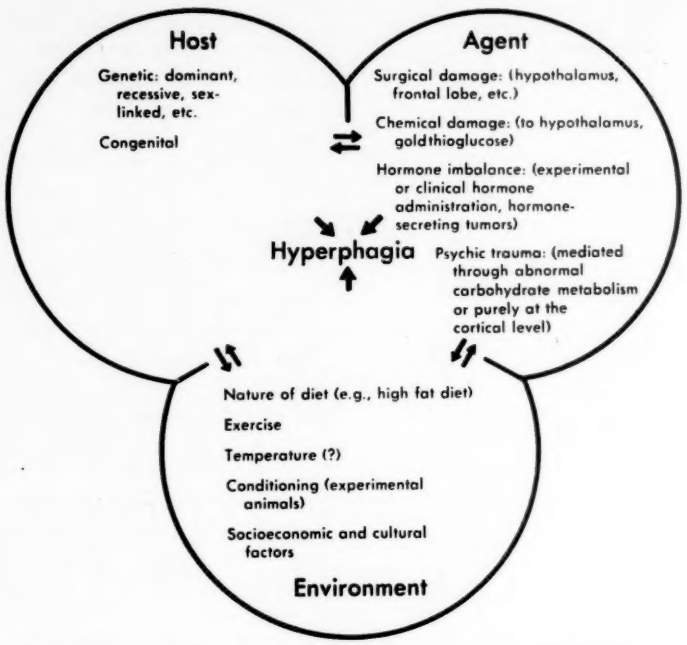
Host
Genetic: dominant, recessive, sex-linked, etc.
Congenital
Agent
Surgical damage: (hypothalamus, frontal lobe, etc.)
Chemical damage: (to hypothalamus, goldthioglucose)
Hormone imbalance: (experimental or clinical hormone administration, hormone-secreting tumors)
Hyperphagia
Psychic trauma: (mediated through abnormal carbohydrate metabolism or purely at the cortical level)
Nature of diet (e.g., high fat diet)
Exercise
Temperature (?)
Conditioning (experimental animals)
Socioeconomic and cultural factors
Environment

FIG. 4. A schematic view of constitutional (genetic and congenital), traumatic and environmental factors in the etiology of obesity. From: MAYER, J. *Postgraduate Med.*, 25: 631, 1959.

proportion appears to be of the order of 40 per cent. If both parents are obese, the proportion rises to 80 per cent. Other investigators have noted that adopted children do not show this pattern, a fact which suggests that environmental factors are not the only ones involved. It thus appears safe to conclude that both genetic and environmental factors are at work.

There are traumatic factors of various sorts which cause obesity in experimental animals and man. We can produce obesity through hormonal imbalances, such as grafting ACTH-secreting tumors in animals.[15] The hereditary obese-hyperglycemic syndrome seems also to represent an endocrine imbalance, that is excessive secretion of insulin and glucagon by the islets of Langerhans. Psychic trauma may cause obesity as well. Experimental animals can be punished unless they overeat. Soon they learn to overeat; if the punishment is removed, they keep on overeating for a while.

Environmental factors are important. The nature of the diet, at least in experimental animals, is not as important as has been often implied, unless proper genetic factors are present. Only certain strains of rats and mice will become extremely obese on high-fat diets.[15] This is a good illustration of the interaction between genetics and environment.

Exercise is tremendously important in experimental animals and in man as well. The reasons for this will be developed later.

Obesity can be classified not only on the basis of etiology (genetic, traumatic, environmental) but also on the basis of the mechanism of development. We have already made a distinction between "regulatory" obesity, in which excessive food intake is due to an error in the central mechanism, and "metabolic" obesity, in which the overeating is a result of an abnormality in the metabolism of fats and carbohydrates.[16]

As an example of regulatory obesity, we may consider the obesity due to destruction of the ventromedial area of the hypothalamus, or to punishing the animals to make them overeat.

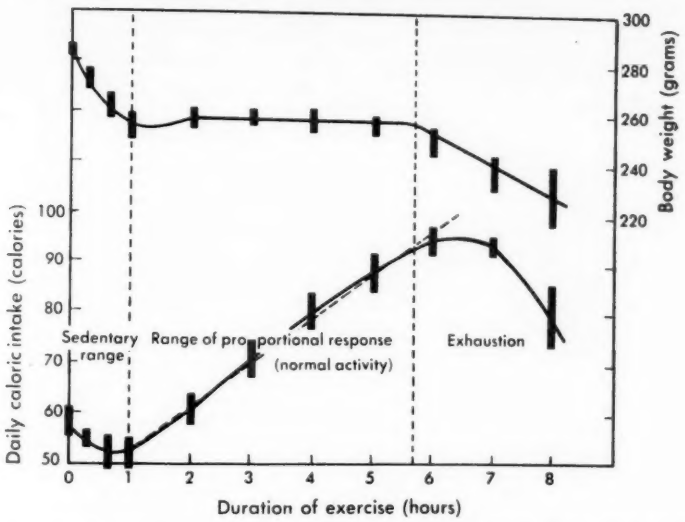

FIG. 5. A summary of laboratory experiments, this graph shows that food intake does not necessarily increase with exercise in experimental animals. Although rats exercised for three or four hours daily eat more than those exercised for one hour, they maintain their body weight because of their activity. However, rats exercised for less than one hour daily or not at all eat significantly more, and weight accumulates because of the increased food intake and low activity level. From: MAYER, J. *Postgraduate Med.*, 25: 329, 1959.

As an example of metabolic obesity, we may consider various types of genetic obesities: the obese-hyperglycemic syndrome, the yellow obesity (both seen in the mouse) and various types of obesities induced by interfering with the endocrine balance of the animals (e.g., mice made obese by the grafting of ACTH-secreting pituitary tumors).

One way in which these can be distinguished is through the study of fat synthesis in the fasted state. If the animals are obese solely because they overeat, lipogenesis reverts to normal when the animals are fasted. This is the case, for example, in mice made obese by the administration of goldthioglucose. If, on the other hand, overeating is the result of metabolic abnormalities, the latter will still be present when the animal is fasted. For example, the obese-hyperglycemic or yellow mice still make more fat than control mice when they are pair-fed or when they are fasted.

EXERCISE

One word on the effect of exercise, a factor which has been grossly underemphasized, particularly in children. The reason often advanced for neglecting exercise as a factor in weight control is that, "it consumes very little energy." This is obviously absurd. We all know you can triple the energy expenditure of human beings by exercising them vigorously enough. Just to give some examples of energy expenditure: an hour's walking is worth 300 to 400 calories in an adult. Swimming vigorously, or playing tennis, is worth about 700 calories per hour.

The other fallacy advanced to justify neglecting exercise is the idea that, "if you exercise more, you eat more, and that therefore, the whole process is self-defeating." We find that this is not true at low levels of energy expenditure. For example, if rats exercise more than an hour, their food intake increases over and beyond their intake corresponding to one hour (and under these conditions, the body weight remains constant). If the length of exercise is further increased, appetite increases until the animal is exhausted and starts eating less. More relevant to the problem of obesity is what happens at the very low

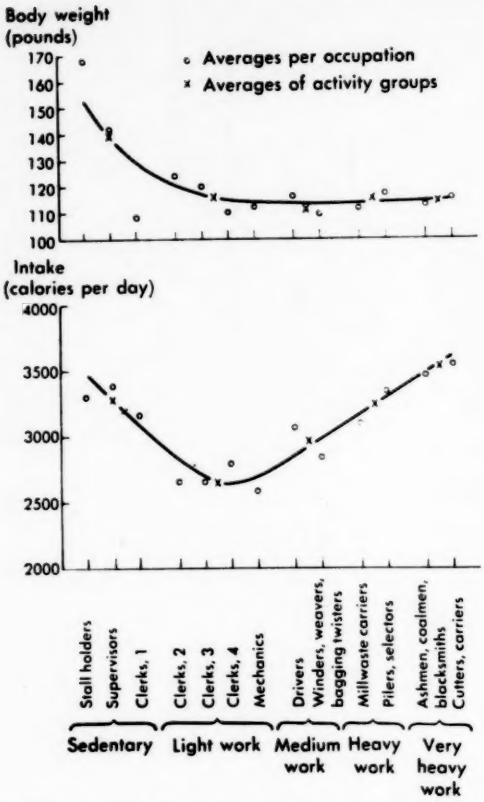

FIG. 6. Results of a study conducted on a population in India, showing the relation of a wide range of activities of food intake and adiposity. Clerks are grouped according to the daily time spent in walking. As in experimental animals, persons who exercised regularly had the lowest daily food intake, those who did heavy work ate more to maintain their weight. Inactive persons also ate more and became obese. From: MAYER, J. *Postgraduate Med.*, 25:330, 1959.

levels of energy expenditure. If exercise keeps on being decreased, a point is reached (one hour) when the food intake no longer decreases. As a matter of fact, it significantly increases again,[17] perhaps because of decreased utilization of glucose under these conditions.[18] This is also true in man (Fig. 5).

A few years ago we made a study in India of the food intake and weight of people whose activities varied from very sedentary to that of extremly hard work (carrying the equivalent of their body weight for nine hours a day). The phenomenon observed there was very similar to the one seen in rats, namely, that the more active subjects are beyond a minimum point, the more they eat; on the other hand, in the inactive range this is no longer true, but rather quite the reverse: the more inactive sedentary people are, the more they tend to eat (and, of course, the weight goes up correspondingly)[19] (Fig. 6).

We find this to be true also among children in the Boston area. To be sure, there are a number of children who eat more than normal and are obese. However, the vast majority of obese children have food intakes which are not only of the same order but often less than those of normal weight children. There is, however, no flouting of the laws of thermodynamics. If you look at the other side of the balance sheet—activity—you find that these obese children differ from the nonobese children in that they are extraordinarily inactive. In a typical group, active sports were practiced less than one-third as much by obese children than by nonobese children.[20] The few data we have on the intensity with which exercise was practiced would further emphasize this difference. Moreover, we find that if we exercise obese children, even without doing anything about their diet, we can in most cases make them lose weight.[21]

It is of interest, incidentally, to note that studies in which "underfed" animals outlived animals fed ad libitum were conducted on caged animals and in effect compared nonobese animals. Results might have been different in exercised animals.

I would, therefore, add one more factor among various social factors which promote obesity, and which were listed by Dr. Forbes, namely, the inactivity which has become associated with Western society. The combination of school buses, television and anxiety about school marks, means that children no longer walk (and in particular do not exercise by simply going to school) and exercise very little after school. I am sure that the increase in the incidence of obesity which we have observed among children in the past eight or ten years in the Boston area is, in large part, due to underexercising as much as to overeating.

SUMMARY

The problem of appetite control will not be attacked rationally until more is known about the mechanism of regulation of food intake. While a general scheme is now available relating gastric contractions to hypothalamic centers and suggesting ways whereby the metabolic state of the organism influence hypothalamic function, much work remains to be carried out on these aspects as well as on the interrelationship of higher centers.

Obesity, like anorexia, can be the result of a great many disturbances in the mechanisms regulating food intake. From the standpoint of etiology one can speak of genetic, traumatic and environmental factors. Genetic factors are of particular interest. A large proportion of children of obese parents are obese, with environment appearing to be responsible only in part. This suggests that preventive programs aimed at children of overweight parents should be started early. Among environmental factors, exercise has been very much underestimated in weight control, both in terms of etiology and therapeutics.

From the point of view of pathogenesis, one can distinguish between regulatory obesity, in which the error lies in the mechanism regulating food intake (e.g., hypothalamic obesity and psychogenic obesity); and metabolic obesity, in which the error lies in carbohydrate and fat metabolism (e.g., obese hyperglycemic syndromes and obesity due to excessive ACTH secretion).

REFERENCES

1. MAYER, J. Obesity. I. Diagnosis. *Postgraduate Med.*, 25: 469, 1959.
2. DUBLIN, L. I. and MARKS, H. H. Mortality among insured overweights in recent years. *Tr. A. Life Insur. M. Dir. America*, 35: 235, 1952.
3. BOWSER, L. J., TRULSON, M. F., BOWLING, R. C. and STARE, F. J. Methods of reducing. Group therapy vs. individual clinic interview. *J. Am. Dietet. A.*, 29: 1193, 1953.
4. STUNKARD, A. J. Untoward Reactions to weight reduction among certain obese persons. *Ann. N. Y. Acad. Sc.*, 63: 4, 1955.
5. MAYER, J. and SUDSANEH, S. Mechanism of hypothalamic control of gastric contractions in the rat. *Am. J. Physiol.*, 197: 274, 1959.
6. ANLIKER, J. and MAYER, J. The regulation of food intake. Some experiments relating behavioral, metabolic and morphologic aspects. *Am. J. Clin. Nutrition*, 5: 148, 1957.
7. FREGLY, N. J., MARSHALL, N. B. and MAYER, J. The effect of changes in ambient temperature on spontaneous activity, food intake, and body weight of goldthioglucose-obese and nonobese mice. *Am. J. Physiol.*, 188: 435, 1957.
8. STUNKARD, A. J., VAN ITALLIE, T. B. and REIS, B. B. The mechanism of satiety: effect of glucagon on gastric hunger contractions in man. *Proc. Soc. Exper. Biol. & Med.*, 89: 258, 1955.
9. FORSSBERG, A. and LARSSON, S. On the hypothalamic organisation of the nervous mechanism regulating food intake. II. Studies of isotope distribution and chemical composition in the hypothalamic region of hungry and fed rats. *Acta physiol. scandinav.*, 32 (Supp. 115): 41, 1954.
10. LARSSON, S. Personal communication.
11. ANAND, B. K. Nervous regulation of food intake. Brook Lodge Symposium on Caloric Balance. *Am. J. Clin. Nutrition*, 8: 529, 1960.
12. STUNKARD, A. J. Studies on the physiology of hunger. II. The effect of intravenous administration of various nutrients on the gastric hunger contractions of a man with severe brain damage. *Am. J. Clin. Nutrition*, 5: 203, 1957.
13. SUDSANEH, S. and MAYER, J. Relation of metabolic events to gastric contractions in the rat. *Am. J. Physiol.*, 197: 269, 1959.
14. MAYER, J. Genetic, traumatic and environmental factors in the etiology of obesity. *Physiol. Rev.*, 33: 472, 1953.
15. MAYER, J. The physiological basis of obesity and leanness. *Nutrition Abstr. & Rev.*, Part I, 25: 597; Part II, 25; 871, 1955.
16. MAYER, J. Some advances in the study of the physiological basis of obesity. *Metabolism*, 6: 435, 1957.
17. MAYER, J., MARSHALL, N. B., VITALE, J. J., CHRISTENSEN, J. H., MASHAYEKHI, M. B. and STARE, F. J. Exercise, food intake and body weight in normal rats and genetically obese adult mice. *Am. J. Physiol.*, 177: 544, 1954.
18. CHRISTOPHE, J. and MAYER, J. Effect of exercise on glucose uptake in rats and men. *J. Appl. Physiol.*, 13: 269, 1958.
19. MAYER, J., ROY, P. and MITRA, K. P. Relation between caloric intake, body weight and physical work in an industrial male population in West Bengal. *Am. J. Clin Nutrition*, 4: 169, 1956.
20. JOHNSON, M. L., BURKE, B. S. and MAYER, J. Relative importance of inactivity and overeating in the energy balance of obese high school girls. *Am. J. Clin. Nutrition*, 4: 37, 1956.
21. STEFANIK, P. A., HEALD, F. P., JR. and MAYER, J. Caloric intake in relation to energy output of nonobese and obese adolescent boys. *Am. J. Clin. Nutrition*, 7: 55, 1959.

Some Psychologic Considerations Concerned with the Problem of Overnutrition

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I WAS very much interested in Dr. Forbes' remarks and in particular his thought-provoking comments on the prevailing cultural attitudes toward nutrition in our society.

When mention was made of the current emphasis upon the child and his welfare in the United States, and indeed throughout western society, I could not help but recall the statement, made by a number of professional people, that our age today is the "Age of the Child." It occurred also to me that other people, including the poet, W. H. Auden, have entitled ours the "Age of Anxiety." (I do not pretend to know whether there is any relationship between these two views.) Certainly the care of the child is of central concern today, and rightly so. Nevertheless, it must be admitted that the concern of adults over some aspects of the care and upbringing of children may at times be carried to the extreme of marked apprehensiveness or intense anxiety. One example of such well meaning but unnecessary concern may be the occurrence of certain feeding problems which have their origins largely in the strong need of some parents to feed their children large amounts of food and particularly to offer infants solid foods at a very early age. Such a trend has, I suspect, been promoted by a number of the forces which Dr. Forbes mentioned.

One of these forces is the almost competitive tendency on the part of some physicians recently[1] to encourage parents to offer solid foods to healthy infants at six weeks, four weeks and even two weeks of age or less. Such a tendency exists despite the fact that it has been demonstrated, I think convincingly, that the infant fed adequately on breast milk or by artificial feedings, with appropriately added vitamins, has virtually no need for additional nutrient materials, including iron, during the first three months of life.[2] In addition, recent statistical studies[3] indicate that offering solid foods to infants during the first several weeks of life does not result in earlier sleeping through the night, which some have believed was the case. When mothers do begin to feed their infants solid food at such an early age, real difficulties may arise in some instances. Most infants under two months of age, and even many under three months, are not ready developmentally to perform the complex physiologic act of managing the tongue and hard palate in such a fashion as to swallow effectively a bolus of solid food.[4] Unless she is aware of this fact, and is prepared for the initial reflex retrusion of such a bolus by the very young infant, an over-eager or apprehensive mother may be led to believe that she is failing in her maternal efforts or that something is wrong with her baby. As a result, some mothers may be driven to urge strongly or even to force the infant to eat. The resistive response of the infant may set off a continuing struggle over feeding, a struggle which might well have been prevented by the delay of a few weeks before offering solid food.

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INDIVIDUAL PSYCHOLOGIC FACTORS

In considering further the psychologic aspects of overnutrition, I would like to begin by distinguishing first of all between hunger and appetite. Dr. Mayer has already given a very scholarly discussion of the adaptive

phenomenon of *hunger*, which appears to be regulated by glucostatic and other physiologic mechanisms. *Appetite* in man seems to be a psychologic phenomenon which ordinarily but not invariably coincides with hunger. Appetite is probably also basically adaptive in nature; it is a much more complex and sensitive phenomenon, however, and can be influenced, positively or negatively, by many stimuli of psychologic as well as physiologic nature. Conditioned reflexes in man, as in Pavlov's dogs, may of course produce salivation and other physiologic preparations for eating in response to sights, odors or sounds associated with food. The phenomenon of appetite, however, derives from psychologic stimuli at higher, principally cortical levels of the central nervous system. Appetite thus involves conscious or unconscious fantasies about food or eating which may at times bear little or no relationship to an actual state of hunger, as determined physiologically.

In the average individual, as Stunkard's[5] work has indicated, a state of increased appetite associated with a sensation of hunger does not occur unless the peripheral utilization of glucose is low. In certain persons, however, appetite or the desire to eat may arise or persist even when peripheral utilization of glucose is high, leading to a dissociation of appetite and hunger and frequently to the appearance of overeating or hyperphagia. The biological function of eating thus may become linked to other needs than that of hunger, particularly emotional needs. In such individuals, hyperphagia may become a central although unhealthy mechanism of adaptation to life stress.

Hamburger,[6] in an important paper on obesity, has discussed extensively the symptom of hyperphagia in adults. He has delineated at least four types: (1) hyperphagia as a response to nonspecific emotional tensions; (2) hyperphagia as a substitute gratification in intolerable life situations; (3) hyperphagia as a symptom of underlying emotional illness, especially depressions and hysteria; (4)hyperphagia as an addiction to food. Many well adjusted persons may of course exhibit temporary hyperphagia in states of tension and depression or in reaction to tragic events. In the obese patients mentioned, however, Hamburger found that the hyperphagia was a deeply fixed pattern of obtaining satisfactions which, for psychologic reasons, could not be gained by these persons in a more healthy fashion through successful interpersonal relationships.

In addition to these and other factors operating to increase appetite, numerous situations exist in which appetite may be decreased, even in the face of definitive physiologic states of hunger. Since overnutrition is the topic at hand, I shall only mention representative examples of such situations. Appetite may, of course, be reduced in advanced states of starvation in children and adults, whereas various physical diseases of debilitating nature may have similar effects. Appetite and hunger may be consciously and intentionally ignored or controlled by certain individuals during fasting, whether for religious, political or other reasons. Serious feeding problems in young infants may, without pathophysiologic causes, proceed to states of marasmus.[7] As Talbot and Lindemann[8] have shown, feeding problems of emotional origin in older children may result in such suppression of appetite, related to negativistic behavior and consequent food refusal, that serious interference with growth and development may occur. Finally, anorexia nervosa, in older children and adolescents, represents a syndrome based on deep psychologic disturbance, involving conscious fears and unconscious frightening fantasies associated with eating, or, in more serious cases, pathologically suspicious or even suicidal attitudes, as Eisenberg[9] and others have pointed out. In such cases, inhibition of appetite and hunger may proceed to lethal lengths without vigorous medical and psychologic intervention.

CULTURAL FACTORS

I should like to turn for a moment from these individual psychologic factors which may influence nutrition and summarize briefly certain sociocultural influences, already indicated by Dr. Forbes and Dr. Mayer. In addition to the influence of modern science and

the pressures of contemporary commercialism upon the eating habits of persons in western society, one is struck by the enormous variability throughout the world in the patterns of food preparation and the standards of taste and edibility. The cultural relativity of mealtimes is also interesting, with marked differences in the number and nature of meals ingested daily in various societies. Standards of feminine beauty of figure may bear considerable relationship to the amounts of food ingested by women. Such standards vary currently from nation to nation and have ranged historically, in Western society, from the ample figures depicted by Greek sculptors to the angular lines of the American "flapper" era. Thus historic forces and ethnic factors, relating to national origin and customs, may combine with regional and family patterns of eating to determine the healthy individual's attitudes toward the nature and amount of food taken, as well as the circumstances under which appetite arises. Climate, geography and the types of food naturally available also contribute to such patterns, as in the Arctic Eskimos who require large amounts of fat to exist in a cold environment.

As the geographic and social mobility of families and individuals has increased in democratic societies, in concert with growing industralization and urbanization, a number of shifts in cultural attitudes toward food and eating have taken place, particularly under conditions of abundance. In such situations, problems of overfeeding, overnutrition and satiety may well arise, as Dr. Forbes has suggested. Such problems may well occur with greater frequency than was the case under more static and less abundant agrarian circumstances which formerly prevailed in western society (and which are still common throughout certain parts of the world). Recent developments emphasizing the interdependence of nations, however, have produced examples of such cultural shifts on a broader, more international basis. In North Africa, for example, cultural standards demand that a mother rear a fat baby in order to be deemed an adequate maternal figure. With the population shifts following World War II, certain such mothers, transplanted to the United States as war brides, found themselves in competition to produce the "fattest baby," with feeding problems at times arising from an infant's resistance to his mother's desperate need to prove herself in this fashion.

THE SYNDROME OF OBESITY

After this rather general and somewhat theoretic background, I should like to speak more specifically on the problem of obesity in childhood as a condition resulting predominantly from overnutrition, with hyperphagia as a prominent feature. The syndrome of obesity in childhood has been most carefully and systematically studied by Dr. Hilde Bruch,[10,11] who has reported on her observations in a series of articles and monographs familiar to many pediatricians. Her early investigations rendered important etiologic clarification in what was then an obscure field of investigation. She showed, for example, that contrary to earlier views endocrine abnormalities of serious nature are rarely involved in childhood obesity. As a result of her studies, it became clear that most cases of obesity in children result from a combination of overeating and physical inactivity, with the fundamental metabolic problem being one of caloric and energic imbalance, involving an excess of "input" "over output." Her later investigations illuminated the psychologic and interpersonal factors contributing to the problems of overeating and inactivity in the child. In her most recent discussion of different types of obesity within the syndrome picture,[10] Bruch has delineated two major categories, which she has termed developmental and reactive in nature.

Children exhibiting the *developmental* type of obesity ordinarily are overweight from early infancy, whether one employs the conventional weight-height percentile curves or grids or the more fundamental criterion of Dr. Mayer—pinching. Some biologic predisposition seems often to be involved in such cases, with a family history of obesity discovered in a number of instances. Such children frequently exhibit precocity of growth in other areas, involving increase in height and early onset of puberty. The most important factor, however, seems to be the

significance of the obesity as a manifestation of a "disturbed way of life" for the particular child within a particular "family frame." Feeding problems are frequently noted, often beginning in early infancy, with the mother frequently showing overconcern for the child's physical welfare, manifested in part by overfeeding. In addition, the parent or parents inhibit the physical activity of the child in the context of their overconcern and overprotection, showing unrealistic fears of harm or death to the child as the result of even healthily independent activity. Increased intake of food and decreased energy output thus consolidate the obese pattern.

Within the family constellation, the significant parent, most often the mother, seems unconsciously to choose this child around which to fulfill certain unhealthy needs. Such a pattern is built around an underlying distrubance in the parent-child relationship, but, more fundamentally, may reflect a failure on the part of the parent to adjust adequately in other areas, including the marital relationship. Gradually the child is cemented into a type of symbiotic relationship, in which the parent keeps the child in a closely dependent state, offering food as a substitute for more basic emotional satisfactions. The child clings to the parent and fears more mature steps toward independent functioning, gradually becoming shy, inhibited, immature, and often helpless and withdrawn. Secondarily, of course, the obesity may increase the child's basic feeling of inadequacy and his social isolation, although the child may come to derive some unhealthy feelings of protection and security from his size and bulk. As the child's development proceeds, the overeating, as an initial response to parental overfeeding and later as a type of substitute gratification, may gradually assume the character of a symptom of an underlying depression or may acquire the significance of compulsive eating or an addiction to food, as described in adults by Hamburger.[6]

A clinical example of the developmental type of obesity is represented by a girl of twelve studied recently by my colleagues and myself.[12] This child was conceived out of wedlock by a markedly obese young woman, with a family history of significant overweight. She placed the child for adoption at less than two months of age. The adoptive mother, a small, thin person, had an intense need to rear a child in order to "make up" to the child for her own unsatisfying childhood, a need previously frustrated because of her own sterility. She was constantly afraid that the infant would die, focussing her overconcern on the infant's nutritional state and offering her large amounts of food, despite her pediatrician's reassurance regarding the baby's health. The infant initially refused feedings negativistically, but gradually began to accept and demand food in inordinate amounts. The mother spoon-fed her until twelve years of age, and continued to call the child "baby," fondling her frequently on her lap like an infant.

As the child grew older, the adoptive mother dedicated her life more and more to the care of this child. Her marital relationship was most unsatisfactory to her because of difficulties both on her husband's part and on her own, and her activities became increasingly involved with the child's feeding, excluding her husband, who finally left the home. As the child became increasingly obese, however, the adoptive mother became critical of her weight and her "ugliness" and consulted numerous doctors. The child was by this time extremely demanding upon the mother, and the mother could refuse her nothing, whether food or playthings. Diets prescribed by physicians thus were of no avail, as the mother became anxious and guilty if the child demanded food. She blamed the doctors whose diets she herself had requested, saying that the child would die if she did not eat.

At twelve years, the girl weighed nearly 200 pounds, and was a withdrawn, negativistic person who ate almost constantly, with greater intake of food, particularly sweets, at times when she was tense or depressed. She showed some superficial desire to lose weight and to be accepted by her peers, but verbalized a fear of becoming ill if she dieted. She had been placed in a convalescent hospital for some months at nine years of age, with the employment of a rigid diet, and had lost 70 pounds. She had subsequently contracted measles, however, and in response to her anxiety and that of her mother, she had regained her weight within a few weeks of returning home. Physically no significant abnormalities other than the obesity were apparent at the time of study, with no evidence of abnormal patterns of hormonal secretion.

The *reactive* pattern of obesity, as described by Bruch, involves frequently an initial

response to a family crisis, such as that occurring around the death of a parent or in relation to a lengthy separation from satisfying parent figures. The child may show reactive hyperphagia, at times associated with inactivity, leading to obesity. The hyperphagia and obesity may not persist, although later life events may evoke repeated similar patterns of temporary response. Such a response may at times become a fixed one; in some cases, however, hyperphagia may alternate with anorexia.

An example from my own experience is that of a five year old boy who had not previously been obese. There was a history of feeding difficulty of resistive nature on the part of the boy, most marked in early infancy. The boy had been somewhat overdependent upon the mother, but otherwise seemed to have adjusted fairly adequately despite frequent and occasionally violent arguments between the parents. After years of such marital difficulty of apparently superficial nature, his parents rather abruptly arranged a legal separation and the boy was given by the court into the custody of his father. The boy felt that he should be with his mother and showed some depression immediately following the separation. He soon began to ingest enormous amounts of food, and over a period of approximately four months gained 45 pounds. Because of the father's difficulty in caring for him, unrelated to his obesity, he was returned to his mother. Within several months after this move, the boy lost virtually all of his recently acquired weight. In this situation, the hyperphagia, in Hamburger's terms, appeared to represent both a nonspecific response to tension and a symptom of depression resulting from the loss of the boy's emotional ties to his mother.

CONTRIBUTING FACTORS IN OBESITY

Although the psychologic factors so far discussed seem to be of central importance, other etiologic influences are of course involved in the picture of overnutrition represented by obesity in childhood. It must be admitted that certain European investigators, such as Juel-Neilson[13] and Quaade,[14] have not found psychologic forces to be involved in the degree reported by Bruch and others. Furthermore, in the experience of certain clinicians, including my own, certain children may exhibit marked hyperphagia, particularly at certain stages of development, but obesity may not develop. In addition, as Dr. Bruch[11] has indicated and as Dr. Mayer has mentioned, even obese children of the presumably developmental type may reach plateaus in which they may not ingest overly large amounts of food, while still continuing to maintain or increase their body weights slightly. Obviously psychologic and interpersonal difficulties leading to hyperphagia and decreased activity, with the assistance of cultural patterns, are only part of the total picture.

Time does not permit a scholarly discussion of the literature bearing upon the multiple etiologic contributions to the development of obesity. Certain studies[6,11] testify to the fact that hereditary or *genic* factors play a role, but only a partial one, in this condition. Physiologic factors of *hypothalamic* nature, such as those involved in the glucostatic mechanisms described by Dr. Mayer in animals, certainly contribute to the phenomena of hunger and hyperphagia in man. So far as I am aware, however, the investigations of Stunkard and his co-workers[5] on obese human subjects have failed as yet to demonstrate any definitive biologic impairment in glucostatic mechanisms. Their studies did indicate, on the basis of glucose tolerance curves in obese persons, that increased rates of glucose removal did appear to occur at times of significant life stresses, particularly those associated with the actual or threatened loss of the emotional support derived from key figures. The possibility of a functional derangement in the satiety mechanisms in such individuals was suggested by these investigators, implicating *metabolic* factors still to be explored in relation to tissue metabolism of fat or carbohydrates.

Although, as indicated earlier, *hormonal* factors in obesity do not appear today to play the large role originally assigned to them, it remains possible that they are still involved in a more subtle and as yet poorly understood fashion.[8] A recent set of developments[15] suggests the further likelihood that sympathetic autonomic stimuli may influence the processes of storage or release of fat in various depots. Perhaps a linkage with genic forces may be

involved in regard to certain inherited patterns of autonomic response.[16] An additional possibility has to do with inborn or constitutional differences in "activity type" of infants, as reported by Fries[17] among others. Such patterns of activity might influence the later energy output of the child. In addition, the early feedback from infant to mother of active or passive responses may affect the mother's handling of the infant, in terms of her own needs for a more quiet or more active baby, as the case may be. For those interested, two excellent and balanced reviews of the variety of etiologic variables involved in the production of obesity have been published recently by Bakwin[18] and Illingsworth[19] in pediatric journals.

TREATMENT OF OBESITY

No discussion of obesity is complete without some consideration of treatment. Today, endocrinologic methods of treatment seem irrelevant in most of the cases of obesity in childhood. Diet of course has received much discussion in recent years in recognition of the influence of hyperphagia in the production of the picture. After much initial enthusiasm, dietary methods seem to be of much less help today than had been hoped by many clinicians. Stuart[2] and others, for example, have underscored the battles which can arise in families as a result of the overstrenuous parental implementation of diets recommended by the physician or by other well meaning counsellors. In addition, Bruch's longitudinal studies[10] would seem to indicate that diets, alone or in combination with recommended exercise, offer little promise in the treatment of the developmentally obese child with associated serious emotional disturbance. Drugs also do not appear ordinarily to be of help in childhood and may complicate the picture as a result of side effects. In such cases, psychologic methods appear most appropriate, involving direct psychotherapy for child and parents in order to help them come to grips with the emotional and interpersonal difficulties which contribute to the picture. Even these methods frequently fail, however, in the more seriously disturbed situations, since the interlocking relationships of unhealthy nature within the family are often of such intensity and tenacity that successful change in the attitudes of the parents and, accordingly, in the weight of the child is impossible.

In the case of the girl described, intensive psychotherapy for child and mother on an outpatient basis was attempted without significant benefit. Hospital admission for some months, with attendant psychologic treatment, did lead to some greater independence and progress in social relationships on the part of the child and did make possible the mother's beginning to come to grips with her own problems. Even with this approach, however, the outlook for long-term response in this case is such that one can hope only for a somewhat more happily adjusted and independently functioning obese girl. The pattern of hyperphagia as a symptomatic response to emotional conflict appeared so firmly fixed in this girl that marked change seemed unlikely. The apparent influence of genic factors in this girl's own family background added to this impression. Children with reactive obesity or those with developmental pictures associated with milder emotional problems appear to enjoy a somewhat better outlook for control of obesity, according to Bruch's findings.[10] With these patients also, supportive psychologic measures, avoiding undue or punitive emphasis on weight loss, appear to be far more wise than vigorous dietary, exercise or drug methods of treatment.

What then is the pediatrician to hope for from a treatment approach to the obese child? Is he to believe that all children with this picture, developmental or reactive in nature, should be referred to the psychiatrist or to a child guidance facility? In my own view, the pediatrician has a significant role to play in the management of obese children. Such a role, however, must be predicated upon a diagnostic set of impressions which can lead the pediatrician to appropriate and reasonable steps. Many although not all of the developmentally obese children described by Dr. Bruch, similar to the one described herein, are seriously disturbed children, mortgaged to a disturbed "family frame" and predisposed biologically

as well to the obese way of life. In such cases, and in cases of severe reactive obesity, particularly those of long standing and involving firmly entrenched patterns of hyperphagia in response to emotional conflict, the pediatrician's role may be a limited one. He will wisely avoid criticizing or scolding the parents or child, recognizing that unconscious forces are strongly involved. He may further attempt to allay anxiety and overconcern and may try to help parents and child discontinue futile struggles over weight control, gradually indicating to them the more fundamental problems related to the child's emotional and social adjustment. With patient work in this direction, avoiding attempts to implant deeper insights for which there is no readiness, he may be able to help them develop motivation for more intensive work toward resolving family problems and permitting greater maturity and independence on the part of the child. Psychiatric consultation or referral at this point may be of significant help, and the pediatrician can support such a step by his close collaboration with psychiatric personnel or facilities.

In pediatric practice, there are certain children with obese tendencies of mild to moderate degree, exhibiting relatively little personality disturbance and living in healthier family situations. Some of these are children who show prepubertal obesity, which may disappear with continued growth and maturation. In such instances, the pediatrician's counsel may help prevent unnecessary anxiety or a battle over weight control, avoiding lasting feeding problems, negativism or other difficulties. In other instances, children of mildly overweight family tendencies or with hyperphagia of only moderate degree may exhibit strong motivation toward weight reduction, particularly as adolescence approaches and heterosexual interests develop. If the pediatrician has an ongoing relationship with child and parents, he may in such situations be able to aid weight control supportively by dietary or other measures.

Let me emphasize once more the involvement of multiple etiologic forces in the syndrome of obesity. These operate in predisposing, contributory, precipitating and perpetuating fashion, and appear to include psychologic, interpersonal, familial and cultural factors, as well as genic, constitutional, hypothalamic, hormonal and metabolic influences.

REFERENCES

1. Prugh, D. G. Psychological and psychophysiological aspects of oral activities in childhood. *Pediat. Clin. North America*, 3: 1049, 1956.
2. Stuart, H. G. and Prugh, D. G. The Healthy Child: His Physical, Psychological, and Social Development. Cambridge, Mass., 1960. Harvard Press.
3. Grunwaldt, E., Bates, T. and Guthrie, D. The onset of sleeping through the night in infancy. *Pediatrics*, 26: 667, 1960.
4. Green, M. and Richmond, J. B. Pediatric Diagnosis. Philadelphia, 1954. W. B. Saunders.
5. Stunkard, A. J., Van Itallie, T. B. and Reis, B. B. The mechanism of satiety. Effect of glucagon on gastric hunger contractions in man. *Proc. Soc. Exper. Biol. & Med.*, 89: 258, 1955.
6. Hamburger, W. W. Emotional aspects of obesity. *Med. Clin. North America*, 35: 483, 1951.
7. Bakwin, H. Loneliness in infants. *Am. J. Dis. Child*, 63: 30, 1942.
8. Talbot, N. B., Sobel, E. H., Burke, B. S., Lindemann, E. and Kaufman, S. B. Dwarfism in healthy children. Its possible relation to emotional, nutritional, and endocrine disturbance. *New England J. Med.*, 236: 783, 1947.
9. Lesser, L. I., Ashenden, J. F., Debuskey, M. and Eisenberg, L. Anorexia nervosa in children. *Am. J. Orthopsychiat.*, 30: 572, 1960.
10. Bruch, H. Obesity. In: Symposium on "Behavior Disorders." *Pediat. Clin. North America*, 5: 613, 1958.
11. Bruch, H. The Importance of Overweight. New York, 1957. W. W. Norton.
12. Prugh, D. G., Harlow, R. G., Conrad, W. G., Allen, J., Weidrich, M. and Locklin, E. A case of obesity treated psychotherapeutically on a children's psychiatric in-patient unit. Presented at the Annual Meeting of American Orthopsychiatric, Chicago, Ill., March 1960.
13. Juel-Neilson, N. On psychogenic obesity in children. *Acta paediat.*, 42: 130, 1953.
14. Quaade, F. On psychogenic obesity in children. *Acta paediat.*, 42: 191, 1953.
15. Marshall, N. B. and Engel, F. L. The influence of epinephrine and fasting on adipose tissue content and release of free fatty acids in obese, hyperglycemic, and lean mice. *J. Lipid Res.*, 1: 339, 1960.
16. Jost, H. and Sontag, L. W. The genetic factor in autonomic nervous system function. *Psychosom. Med.*, 6: 308, 1944.
17. Fries, M. E. The psychosomatic relationships

between mother and infant. *Psychosom. Med.*, 6: 159, 1944.

18. BAKWIN, H. Obesity in children. *J. Pediat.*, 54: 392, 1959.
19. ILLINGSWORTH, R. S. Obesity. *J. Pediat.*, 53: 117, 1958.

DISCUSSION

DR. GILBERT B. FORBES (*Rochester, New York*): I should like to ask Dr. Mayer to elaborate just a bit on a matter which he mentioned briefly in his presentation. What about the matter of basal metabolic rate in obese children? Moreover, is there any evidence for abnormal utilization of food or metabolic abnormalities in the obese child?

DR. JEAN MAYER (*Boston, Massachusetts*): First of all, as regards basal metabolic rates, I would like to emphasize the fact that these are very difficult to interpret in obese subjects, particularly in obese children. This is quite understandable if you consider the way in which the tables were established. The tables were established so as to fit large numbers of individuals who did not have thyroid disease.

At the Children's Hospital in Boston, Dr. Heald has been making a study of obese children who had been treated with thyroid medications by their physician because of decreased basal metabolic rate. He finds that the great majority of these children do not have any abnormality of thyroid function on the basis of such pertinent criteria such as serum protein-bound iodine, radioiodine uptake, and so on.

Regarding the possibility that obese subjects may handle their metabolites poorly, I would say, based on experiments in animals, that I am committed to the idea that there are a great many different forms of obesity, that obesity is the end product of a great many conditions which may have very little in common, just as fever is. Therefore, I would anticipate that for many subjects in whom there is something basically wrong with the mechanism of regulation of food intake, either physiologically or psychologically, there is no abnormal handling of metabolites. On the other hand, however, there are subjects in whom I would expect an abnormal handling of metabolites. We are working at present on a clinical test to distinguish between those two types.

In experimental animals with regulatory obesities, as in normal animals, we have observed that there is an increase in blood ketones when the animal is fasted. In the various types of metabolic obesities, in which there is a basic disturbance in fat metabolism, we do not find this. In fact, we often observe a decrease of blood ketones when the animal is fasting.

We have only very preliminary results in man, both in adults and in children, but we find that here, too, there appear to be two classes of obesity: a majority in which you find a normal rise in blood ketones when the individual is fasted, but a large minority—perhaps 30 per cent—in whom the blood ketones do not rise and may even fall during fasting. Those presumably represent metabolic obesities. In our cultural setup, however, I would not expect to find basic metabolic abnormalities in the majority of obese children, although I think we are finding it in a minority.

DR. KURT SCHREIER (*Heidelberg, Germany*): I should like to add a few words to the discussion. We in Heidelberg have made studies on about 150 obese children using the glucose tolerance test, insulin test, pyruvic acid level, proteins, and so on.* We did not find any significant changes from the normal range. The only thing we found was hypercholesterolemia. This finding is nothing special because the children eat too much fat and synthesize more cholesterol from acetic acid. We in Europe are inclined to disagree with Professor Wertheimer when he speaks of lipophilia of the organism. It is for that reason that we began to study all our obese children. We think there is no lipophilia whatever.

QUESTION: Dr. Mayer stressed the importance of underactivity as a cause for obesity, whereas others are more or less convinced that overeating is the major cause. Would Dr. Mayer comment further on this matter?

DR. MAYER: I should like first to comment on what Dr. Schreier said. The relationship of obesity to cholesterol is an extremely complex one. In experimental animals there are certain types of obesity which are associated with marked hypercholesteremia, the blood cholesterol being three to four times the normal. These include the obese hyperglycemic mice, mice with ACTH-secreting tumors and female yellow mice. On the other hand, in the "regulatory" hypothalamic obesities, the blood cholesterol level is normal or only slightly elevated.

The idea that different fatty tissues have different characteristics is a very important concept. Renold and others have clearly confirmed what Wertheimer first indicated, namely, that in some forms of obesity the adipose tissue is perfectly normal, but that in other forms it is quite abnormal in its metabolism of certain substrates, such as acetate and pyruvate.† Again, I think it is dangerous to think of obesity as *one* condition.

The effect of activity is demonstrable only when you have an active population. It is also obvious that in very inactive populations the factor of overeating is the only one you can demonstrate. In the United States adults by and large are so inactive that overeating, as such, is more important than activity. However, Stunkard has shown in pedometer studies

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* SCHREIER, K. Adipositas im Kindesalter. *Deutsche med. Wchnschr.*, 84: 1297, 1959.

† CHRISTOPHE, J., JEANRENAUD, B., MAYER, J. and RENOLD A. E. In vitro metabolism of adipose tissue in obese-hyperglycemic and goldthioglucose treated mice. I. Metabolism of glucose. *J. Biol. Chem.*, in press. Ibid. II. Metabolism of pyruvate and acetate. *J. Biol. Chem.*, in press.

that obese women may exercise only about one-third as much as nonobese women.

In children, our main experience is with adolescents. Adolescence is a period in which most people are very active. The food intakes of normally active adolescents may be enormous. We are no longer dismayed or surprised when we find adolescents with food intakes in excess of 6,000 calories. By comparison with the very active adolescents, most obese adolescents do not eat that amount. This is not to say they do not take in more calories than they expend.

QUESTION: What about the importance of the family eating habits, and the pattern of carbohydrate and fat in the diet?

DR. MAYER: We have no data which would lead us to believe that in the Boston area the choice of foods of obese patients is very different from that of nonobese patients.

We find that (on a large sample, which again may eliminate differences between different types of obesity) underweight, normal weight and overweight adults eat the same proportion of carbohydrate and protein. We find very little difference in the types of meals and distribution of meals until five o'clock in the afternoon. In obese adults most of the overeating is done at the evening meal, and at night.*

In the case of children, workers in Iowa have found there is a tendency for obese children to eat more carbohydrate and a little more fat than normal children; but it is a very small difference.† Whether it is causal to the obesity is doubtful. Again we are dealing with a population which has a very high protein intake in general.

QUESTION: Many physicians, particularly in Europe, find that overweight children take an overdosage of calories in the morning. We also find that it is almost impossible to change the basic eating habits of our patients. Is this also true here in America?

DR. MAYER: I would say this: The treatment of obesity has to be on a long-term basis. Short-term treatment means nothing. Treatment really begins when the patient and his family have accepted the idea that what they have to do is actually change their mode of life—food habits, exercise habits and general outlook.

One of the things I do not like about either the "miracle" reducing cures or drug treatments is that they are predicated on the idea that obesity is a short-term problem, that you can do something about it in a few weeks; when in fact, it is a lifetime problem.

DR. FORBES: I should like to ask Dr. Prugh to comment on the matter of attempting to change food habits which have become deeply ingrained over the years. I should also like to direct another question to him, and this concerns the tacit assumption among pediatricians that the fat child should be made to reduce by one means or another. Does one ever harm a child by forcing a weight-reducing regimen on him, whether this be diet, exercise or drugs? Does one always come up with a desirable end product, or are there patients who might be worse off after weight reduction than before?

DR. PRUGH: I would like to respond to the last question first, in regard to the possibility of any harm to the child which might be produced by a reducing regimen. As I implied earlier, the degree of healthiness of the motivation of child and parents toward weight reduction is the most important factor in determining the response to weight-reducing measures. In some instances in which motivation is relatively healthy and in which contributory or complicating biological, psychologic and interpersonal influences of a seriously unhealthy nature are minimal, the use of such measures can succeed. In certain other instances, however, the parents are not dissatisfied with the child's weight, which may parallel their own. Consequently, the physician's weight and height standards mean nothing to them in the light of their own family attitudes toward obesity, even though no serious emotional pathology is involved.

In more deeply pathologic situations, such as the case described herein, weight reduction simply fails if the contributory problems cannot be resolved, even if child and parents superficially wish for weight reduction. Such parents and children may find reasons not to adhere to the recommended diet or exercise, may simply continue their battle over food, or may drift away from the physician if he continues to urge them to adhere to the measures which they themselves requested. Some children, as in the case cited, have a paradoxic and usually unconscious fear of losing the "protective wall" of weight, as Bruch has indicated, and may resist diets on these grounds as well as others. In a few, very disturbed family situations, the use of strong exhortation may drive the child and parents to successful implementation of dietary measures, at least on a temporary basis. This may break down, however, and sudden regaining of weight occur, or occasionally the older child or adolescent may become depressed or anxious if deprived of the use of food for substitute gratifications.

In the latter, relatively rare situations, in my experience, the overstrenuous imposition of a diet may bring actual psychologic harm to the child. In older adolescents and adults, this phenomenon is more familiar, as reported by Hamburger,‡ Stunkard§

* BEAUDOIN, R. and MAYER, J. Comparative study of various methods of dietary intakes of obese and nonobese women. *J. Am. Dietet. A.*, 29: 29, 1953.

† EPPRIGHT, E., SIDWELL, V. and JEBE, E. Food intake and body size of Iowa children. In: Weight Control, pp. 119. Iowa State College Press, 1955.

‡ HAMBURGER, W. W. The psychology of weight reduction. *J. Am. Dietet. A.*, 34: 17, 1958.

§ STUNKARD, A. J. The dieting depression. Incidence and clinical characteristics of untoward responses to weight reduction regimens. *Am. J. Med.*, 23: 77, 1957.

and others. In some seriously disturbed persons, the hyperphagia may have become such a fixed and internalized pattern of dealing with conflict or tension that the successful employment of a diet, through exhortation, shaming, frightening and other methods of pressure, may precipitate serious depression, with occasionally even suicidal implications. In such instances, the use of a diet in the manner described seems clearly contraindicated.[9] With children strong contraindications would apply to a few very seriously pathologic family equilibria. In many other instances, however, extreme caution and an avoidance of overstrenuous measures are exceedingly important, with concentration on other approaches to the resolution of the underlying psychologic and interpersonal difficulties.

Regarding Dr. Forbes' other thought, I think most girls in our society today have some concern about their body weight. Our idea of the feminine figure is not quite the same as it was in the 1920's, the "flapper" days. Being thin like the models in the magazine advertisements, however, does mean a great deal to many adolescent girls, and much concern may be mobilized unfortunately over the picking up of a few pounds of weight.

Some Consequences of Overnutrition with Minerals

D. Mark Hegsted, ph.d.*

It is difficult to know exactly what is meant by overnutrition. I assume we can eliminate such things as lead poisoning, but I am not sure whether chronic toxicity of essential minerals such as copper, iron or zinc is really any different from hypervitaminosis.

This topic is somewhat difficult because there are not many good clinical examples of overnutrition with minerals. Therefore, we will have to rely partly upon animal experiments and partly upon supposition.

Moreover, I find myself talking a great deal about overnutrition with calcium. This, in itself, is a little peculiar because nutritionists have spent the last twenty or thirty years vigorously promoting the consumption of higher levels of calcium throughout the world. In the United States, it is claimed that calcium deficiency is the primary nutritional deficiency in the population, that is, that some 30 per cent of the people in the United States fail to receive adequate amounts of calcium.[1,2] Now, if we do not have the highest intake in the world, we come very close to it; and if our nutritional status is poor because of low calcium intakes, I should think the rest of the world would have collapsed long ago.

On many occasions I have said that our nutritional standards for calcium are based on a false interpretation of the data. They are based on calcium balance studies which really give no indication of calcium need. They simply measure dietary habits.

Despite all the talk about calcium and the promotion of greater calcium intake, calcium deficiency, from the clinical standpoint, is still to be demonstrated. If it were a major problem, one might expect that calcium deficiency in many parts of the world would be very well defined clinically.

Of the things I have in mind that might be called overnutrition with minerals, perhaps fluorosis is the best example. The effects of high fluorine intake on teeth are well known. It is very unfortunate that the toxic effects of fluorine both in man and in animals were well known before the beneficial effects on dental caries were demonstrated. It is now well documented that when fluoride is added to water supplies at appropriate levels, with adequate control, there are absolutely no detrimental effects, and at the same time there is at least a 50 per cent reduction in dental caries. To me it seems practically criminal that so many people still fail to receive adequate amounts of fluorine because of opposition not based on scientific facts. Certainly, one of the efforts of all medical people should be to promote fluoridation wherever it is needed.

Another good example in animals is molybdenum toxicity. In certain areas of the world it has been shown that the molybdenum intake of various species is too high and that this promotes copper deficiency.[3] That is to say, in areas of high molybdenum intake a higher copper intake is required, or in other words, copper counteracts molybdenum toxicity. We do not know whether this has any implications in man. At least it is an example of an interaction between two essential nutrients, and perhaps more studies into the role of trace elements—studies that are only now beginning—will demonstrate relationships of this kind in human nutrition. Man is protected, to a considerable extent, from toxicities

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of this kind because his food supply is diluted out in the commercial market and usually comes to him from many areas rather than limited locations that have particular soil characteristics.

Another interesting example in animal nutrition that has been demonstrated only recently is zinc deficiency in swine. Ordinarily, a diet containing 30 to 40 parts per million of zinc is adequate for swine; but when the calcium level is raised to approximately 1 per cent, zinc deficiency develops, characterized by a severe parakeratosis.[3,4] It can be prevented, or cured, by either adding zinc to the diet or by decreasing the calcium in the diet. Again, we do not know whether this particular example is relevant to human nutrition, but it indicates some of the interrelationships that we may have to worry about. There is experimental evidence indicating that high calcium diets effect the utilization or requirement of several other minerals. These include iodine, iron, magnesium, manganese and, of course, phosphorus.[4,5]

With regard to calcium, perhaps the first thing that occurs to us is the relation of calcium to the hypercalcemia syndrome of infancy which has become so important recently in certain parts of the world. I suppose hypervitaminosis D is the most likely cause, although it still seems to be an inadequate explanation; and it is likely that high calcium intakes may be a contributory cause.

There is abundant experimental evidence to show that vitamin D toxicity, in animals at least, depends upon calcium intake. I think all studies on vitamin D toxicity have shown that high calcium diets increase the relative toxicity of vitamin D. We need, very badly, some quantitative evidence on the relative role of calcium and how important this may be.

The most important indication that calcium may be involved in idiopathic infantile hypercalcemia is that low calcium diets are of value therapeutically. For this word "idiopathic" it seems to me we should substitute "ignorance." It might help us in getting to the root of some of the problems we really want to know about.

Another area in which calcium may be involved is kidney stones. This possibility also has been demonstrated by a number of experimental studies, but the primary evidence would be simply that, therapeutically, low calcium diets seem to be called for. When a stone begins to form, it seems only logical to decrease the urinary calcium; one way to do this, of course, is to adhere to a low calcium diet. It seems to me that calcium intake cannot be the only etiologic factor in renal stones. There are many areas in the world where calcium intake is low but renal stones are common. I think we must assume that this is a complex etiologic problem of which calcium intake may be one facet.

In studies with animals in our department, we[6,7,8] have been able to show that on pyridoxine-deficient diets, the urinary excretion of oxalate is high. Under these conditions, with a high urinary level of oxalate, it is very easy to demonstrate that the calcium level in the diet is important and accentuates stone formation.

There is also some evidence in presumably well fed persons that treatment with pyridoxine will lower the excretion of oxalate.[8] Whether this indicates a pyridoxine deficiency or whether it is of relevance to kidney stones or oxalate stones in human beings, remains to be demonstrated.

Another area in which we might implicate calcium is in the milk-alkali syndrome. Again, this condition cannot be caused by a high calcium diet alone although it does emphasize that, under certain conditions, high calcium diets may be detrimental.

Many studies indicate that there are probably no universal nutritional standards and that the need for any particular nutrient depends upon many factors. We all know that physiologic function, growth, pregnancy and lactation, for example, are primary factors in influencing nutritional requirements. Numerous studies, both in animal and in human nutrition, indicate that various factors in the diet also influence nutritional requirements for others. Some of these I have alluded to, but there are many others that demonstrate that vitamin and mineral requirements are a func-

tion of the kind of diet and the level of intake of various other nutrients. Obviously studies are necessary in various parts of the world where the basic diets are different. It is doubtful that uniform standards will be satisfactory for all different nutritional conditions.

We have spent many, many years urging higher and higher intakes of various kinds of nutrients. In large part, this emphasis has been due to the so-called "margin of safety" that we allow to cover our ignorance. We all agree that people should not be kept on minimal levels of nutrition, but we have little scientific basis for estimating an adequate margin of safety. Also, it is time that we realized that the margin of safety must apply at the top as well as at the bottom in setting nutrition standards. Optimum nutrition, if I can define it, is somewhere in between too little and too much; and the definition of it really is our major problem in nutrition.

REFERENCES

1. Phipard, E. F. Agricultural Handbook, No. 56, 1952.
2. Ohlson, M. A., Kelley, L. and Quackenbush, G. G. Michigan State University, Agricultural Experiment Station, Technical Bulletin No. 258, July 1956.
3. Underwood, E. J. *Ann. Rev. Biochem.*, 28: 499, 1959.
4. Davis, G. K. *Fed. Proc.*, 18: 1119, 1959.
5. Davis, G. K. and Loosli, J. K. *Ann. Rev. Biochem.*, 23: 459, 1954.
6. Gershoff, S. N., Faragalla, F. F., Nelson, D. A. and Andrus, S. B. *Am. J. Med.*, 27: 72, 1959.
7. Andrus, S. B., Gershoff, S. N., Faragalla, F. F. and Prien, E. L. *Lab. Invest.*, 9: 7, 1960.
8. Gershoff, S. N., Mayer, A. L. and Kulczycki, L. L. *Am. J. Clin. Nutrition*, 7: 76, 1959.

DISCUSSION

Dr. Gilbert B. Forbes (*Rochester, New York*): Dr. Hegsted is the first speaker to mention the word "optimum" as applied to nutrition. I was happy to hear it used, although Dr. Hegsted admitted that he could not define it in precise terms.

There is one situation in human nutrition in which we can, with some degree of certainty, point to an optimum level of a dietary constituent. I refer to the work of Hodge* on fluoride intake in man (Fig. 1). As the intake of fluoride in the drinking water increases, there is a decline in the severity of dental caries; but if the intake rises above a certain level toxic symptoms, namely, mottled enamel, begin to appear. The junction of these two lines suggests that a level of one part per million in the drinking water provides an *optimum* intake of fluoride.

Perhaps if we had more such diagrams for other dietary essentials, we would be a little closer to a definition of optimum as it applies to nutrition in general.

Dr. L. E. Holt, Jr. (*New York, New York*): I would like to ask Dr. Hegsted if he thinks there is any place for molybdenum-iron in therapy.

Dr. Hegsted: When I first heard about this, I tried to look it up in the literature, and concluded it was a "gimmick"; I might be wrong.

Dr. Forbes: The term "hypercalcemia" was mentioned by Dr. Hegsted. Dr. Stapleton, do you have any comments on the infantile hypercalcemic syndrome and related problems?

Dr. Thomas Stapleton (*London, England*): Just a few thoughts occurred to me. First of all, it is a well known fact that among the people who were unfortunate enough to be prisoners in places in which there was not much food for them in the last war, those who started off as thin chaps survived better than those who started off as fat chaps.

In discussing calcium, Dr. Hegsted, I think it is frightfully important that one does not become too interested in just a mineral, because I am sure that the effects of the amount of calcium in the diet and the requirement for it depend very much on the protein intake of the individual.

Recently, we had a meeting to discuss and recommend the level of vitamin D fortification of infant foods in England; we chose 400 I.U. a day.† All I can say about the effects of our recommendation is that the British Paediatric Association this year is conducting a new survey of the incidence of hypercalcemia and of rickets in the United Kingdom and Northern Ireland. One hopes that at the end of the year the number of children with each disease will be equal; then one will consider that stating the requirement at 400 I.U. must have been a fairly reasonable figure.

Dr. Kurt Schreier (*Heidelberg, Germany*): I should like to mention only briefly that there is a disease called "Kaschin-Beck" syndrome around the Baikal lake area in Russia. Some investigators believe that it is due to overnutrition with iron.

Dr. Forbes: Dr. Harrison, do you have some comments on the calcium problem?

Dr. Harold Harrison (*Baltimore, Maryland*): I agree with Dr. Hegsted that the dietitians' and nutritionists' concern about calcium deficiency in this country seems highly overdone. It is hardly likely

* Hodge, H. C. The concentration of fluorides in drinking water to give the point of minimum caries with maximum safety. *J. Am. Dent. A.*, 40: 436, 1950.

† Editor's note: This represents a lower figure than that previously recommended, and it is of interest that the incidence of infantile hypercalcemia in Great Britain is now on the decline.

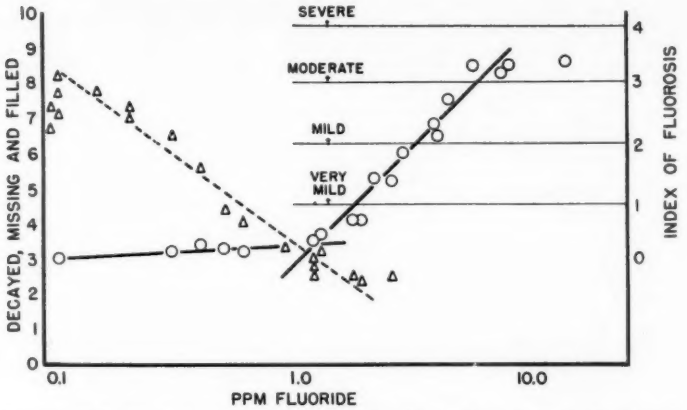

FIG. 1. Relation between water-borne fluoride, index of fluorosis and the number of decayed, missing and filled teeth. From: HODGE, H. C. *J. Am. Dent. A.*, 40:436, 1950.

that there is any serious calcium deficiency in this country. On the other hand, I am not convinced that the problem of overnutrition of calcium in this country has been demonstrated either. Certainly, high intakes of calcium are common, but all our evidence would seem to suggest that adaptation to such high calcium intakes, if the calcium is in the form of milk, is apparently good, and that when dysadaptation occurs, it is not because of the high calcium intake *per se*, but because of some other factor as in, for example, the milk-alkali syndrome Dr. Hegsted alluded to, or, perhaps idiopathic hypercalcemia. Some other factor has to be adduced besides the high calcium intake.

Perhaps we should look into such things as these: what makes adaptation possible, and why is adaptation to high calcium intakes no longer possible under certain circumstances.

DR. FORBES: I would like to ask Dr. Hegsted and Dr. Harrison if it is known why human breast milk contains so little calcium.

DR. HARRISON: This, of course, has been the reason why the National Research Council has been concerned about calcium requirements in infants, since, if they set up calcium requirements on the basis of balance studies, as Dr. Hegsted has pointed out, it would immediately rule out breast milk as a form of feeding for human infants. They tried to avoid this, however this does not necessarily prove that high calcium intakes are completely unphysiological for the infant. It may merely mean that the human mother cannot adapt to putting out such tremendous amounts of calcium in her milk as the cow. It may be that by the evolutionary process a nice compromise was reached, in other words, an amount of calcium which the mother could lose in her milk per day and yet just be enough for the human infant. It is not necessarily complete evidence that this is the optimal or the only type of calcium intake a human infant should have.

DR. HEGSTED: I do not really have anything more to add to what Dr. Harrison has already said, although I think you will find that the National Research Council did rule out breast milk as adequate by the calcium allowances. It was on the protein allowances that they failed to come to any agreement. However, the old allowances implied that breast milk was inadequate in protein for infants.

I also would like to support what Dr. Harrison said, namely, that I am not very concerned about high levels of calcium intake. We do not really have much evidence that they are bad, except under certain conditions. I would like to emphasize, however, that we have just as much reason to worry about high intakes as we do low ones, particularly when we find intakes of the order of 3 and 4 gm. a day. This sounds high enough for me to be concerned.

DR. HERBERT SARETT (*Evansville, Indiana*): I would like to add to what Dr. Hegsted has said in connection with the availability of various minerals from different diets or foods. He gave some examples of this. These can be extended to include zinc, based on our experiments in chicks, in which the availability from soybean is much less than it is from casein. The manner in which the soybean is processed may also affect the degree of utilization of its zinc.

Therefore, in discussing dietary mineral requirements, the effect of different types of diets and different sources of the minerals must be taken into consideration.

DR. FORBES: There is one important dietary element which Dr. Hegsted did not mention which needs some comment. There has been a lot of talk recently about the relationship between sodium intake and hypertension in adult man, and some experimental work along similar lines in the rat. Dr. Darrow, would you comment on this matter? Are we feeding children too much sodium chloride?

DR. DANIEL C. DARROW (*Kansas City, Kansas*): I have nothing that is really relevant. I am not inclined to apply experimental data on rats or observations on sick children to healthy infants. Hypertension accompanying high intakes of sodium chloride is associated with desoxycorticosterone or presumably high production of aldosterone. However, the normal infant can handle the likely intakes of sodium chloride. I do not believe we ordinarily give foods containing harmful amounts of sodium chloride.

There has been a tendency to prescribe too much sodium chloride in heat stress and in diarrhea when obvious dehydration is not present. I think extra salt is seldom indicated in heat stress when the infant eats. While salt may be added to water when starvation is indicated to decrease stool volume in diarrhea, the concentration should probably not exceed 25 mEq. per L. It is not certain that these mixtures do not sometimes increase stool volumes.

DR. FORBES: Why does human breast milk contain so little sodium (only 7 mEq. per L. in contrast to 25 mEq. per L. for cow's milk)?

DR. DARROW: Obviously the human infant has survived on a low intake of sodium chloride for a long time. Human milk certainly provides an adequate intake. One may speculate that the low intake is, or was, advantageous during the period of adaptation to the environmental conditions of early evolution. The importance of sweat glands suggest a hot, relatively dry atmosphere but an environment providing water. Infant sweat is normally low in sodium and chloride. Consequently human milk provides sufficient sodium for high extrarenal losses of water containing little sodium.

Some Implications of Amino Acid Supplementation

A. E. HARPER, PH.D.*

ANY discussion of this subject must start with the knowledge that for the past fifty years amino supplementation has been used successfully in animal experimentation to stimulate growth and to improve the biologic value of dietary proteins. The value of amino acid supplements was first demonstrated by Wilcock and Hopkins in 1906,[1] when they discovered that the amino acid, tryptophan, was an essential dietary component. It was established with certainty during the next ten years through the extensive studies of Osborne and Mendel[2] on protein nutrition. In the succeeding years, we have seen demonstration after demonstration of the benefits that may be obtained in experiments on animals from the judicious use of amino acid supplements.[3,4]

Why, then, is there any need to discuss the implications of amino acid supplementation? There are two main reasons: (1) the successful use of amino acid supplementation depends upon an accurate knowledge of the type of diet being consumed by the subject receiving the supplement, and (2) under some circumstances, amino acid supplements may not only be of no benefit but may actually cause adverse effects.[5–7]

A great deal of attention today is centered on the significance of the proportions of amino acids in diets or, as it is frequently referred to, the amino acid balance of the diet. The term "amino acid balance" refers only to the proportions of the essential or indispensable amino acids, because all proteins provide sufficient amounts of the nonessential or dispensable amino acids.

For normal performance, different quantities of the individual indispensable amino acids are required. Therefore, if the requirement for tryptophan, the amino acid required in least amount, is taken as one, amino acid requirements can be expressed as a proportion as shown in Figure 1 which is taken from a paper by Flodin.[3] The black bars represent the relative amino acid requirements of the rat. A similar figure, with slight modifications, can be prepared for the human infant, or for any other species. The shaded bars represent the relative quantities of the indispensable amino acids in the proteins of meat, milk and eggs. These proteins provide the indispensable amino acids in roughly the proportions in which they are required by the body. They are, therefore, said to be well balanced proteins, and they are used very efficiently.

Figure 2 shows a comparison of the amino acid proportions of wheat proteins and the proportional amino acid requirements of the rat.[3] Again, the black bars represent the proportional requirements; the shaded bars the relative quantities of the indispensable amino acids in wheat proteins. Such proteins are low in lysine. They are, therefore, said to be unbalanced or poorly balanced. They are not used efficiently by the body.

The efficiency of utilization of unbalanced proteins can be improved by amino acid supplementation. Also, the amino acid requirements of a subject can be met by increasing the total intake of such proteins.[8] This point is easily lost sight of in discussions of amino acid balance and amino acid proportions. We do not necessarily need to consume

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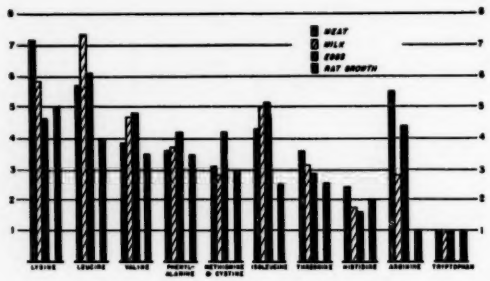

FIG. 1. Amino acid proportions in high quality proteins (calculated on the basis that tryptophan = 1.0). Amino acid proportions in meat, milk and egg protein compared with proportions utilized in rat growth. From FLODIN, N. W. *J. Agr. Food Chem.*, 1: 222, 1953.[3]

food that is completely balanced. For example, if 25 gm. of egg proteins are needed to satisfy the amino acid requirements of a subject, and if protein A contains only half as much of one of the essential amino acids as the well-balanced whole-egg proteins, the amino acid requirements of the subject can be met by feeding twice as much, 50 gm., of protein A. It is, of course, possible for the amino acid balance of a protein to be so poor and the concentration of protein in a foodstuff to be so low that the subject cannot eat enough of it to satisfy his amino acid requirements. It is also possible, if the amino acid balance of a protein mixture is sufficiently poor, that some adverse effect, such as a depression in food intake or in the efficiency of protein utilization, may occur.[9]

Adverse effects of this type can readily be demonstrated in animal experiments in the laboratory as shown in Table I. The basal diet used in this experiment was a highly purified diet containing adequate quantities of vitamins and minerals, 6 per cent of alcohol-extracted casein, 0.3 per cent of DL-methionine, 5 per cent of corn oil and the balance carbohydrate, either sucrose or gelatinized cornstarch (dextrin).

The growth of rats fed this diet is limited primarily by a deficiency of threonine; therefore, supplementation with a small amount of threonine or gelatin stimulates growth. Gelatin, of course, lacks tryptophan which is also low in the basal diet; so, as the quantity of gelatin in the diet is increased, the amino acid pattern of the diet is thrown more and more out of balance. When 12 per cent of gelatin is added, we have a diet containing 18 per cent of poorly balanced protein. The growth rate of rats fed this diet is well below that of rats fed the diet containing only the 6 per cent of quite well balanced protein. We attribute the growth retardation to an amino acid imbalance. It is corrected by a supplement of the most limiting amino acid, in this case tryptophan. It can also be corrected by increasing the amount of well balanced protein in the diet.

Occasionally, amino acid imbalances occur when low protein diets are supplemented with relatively small quantities of amino acids other than the one which is most limiting in the diet.[5–9] An example is shown in Table II. Again a highly purified diet similar to the one mentioned previously was used, but this one was deficient in niacin and contained 9 per cent of casein as the entire protein source. Rats fed this diet grow about 10 gm. a week. Supplementation with methionine gives a very small improvement in growth. Supplementation with threonine alone gives no improvement at all. When methionine and threonine are added together growth is retarded. Apparently additional threonine increases the need for tryptophan because the condition is corrected by a small supplement of tryptophan.[5]

USE OF AMINO ACID SUPPLEMENTS

Such observations, and there are quite a few other examples, have led to the assump-

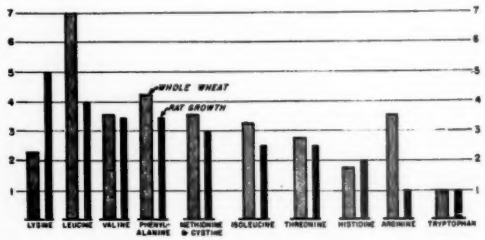

FIG. 2. Amino acid proportions in whole wheat protein (calculated on the basis that tryptophan = 1.0) compared with proportions utilized in rat growth. From FLODIN, N. W. *J. Agr. Food Chem.*, 1: 222, 1953.[3]

tion that amino acid supplementation is a risky process. How well justified is this assumption? There are certainly grounds for exercising caution in the use of amino acid supplements, but I do not believe that there is cause for alarm.

A subject whose amino acid requirements are satisfied can tolerate a diet with quite a poor amino acid balance. Also, the quantities of amino acids required to produce toxic effects—and we can produce toxic effects with large quantities of many of the individual amino acids—are far beyond what could rationally be recommended as a supplement.[8]

What, then, are the cautions that should be observed in the use of amino acid supplements? And what are the possibilities of obtaining beneficial responses from amino acid supplementation?

If we begin with the well nourished subject who is receiving sufficient protein to meet his amino acid requirements, no benefit can be expected from supplementation of his diet with either amino acids or intact protein. The excess can serve only as a source of calories. Subjects receiving adequate quantities of all of the individual amino acids, also, can tolerate a considerable excess of many of the others, an excess of methionine, perhaps, being the least well tolerated. So, there is not much likelihood of causing adverse effects in well nourished subjects unless the intakes of individual amino acids are greatly excessive.

What, then, about the malnourished subject? Here the problem is more difficult. If his over-all protein intake is low, he will be consuming inadequate quantities of several amino acids. Therefore, supplements of several amino acids would be needed to improve his diet very much. The experiment summarized in Table II illustrates such a situation. The diet used in this experiment contained 9 per cent of casein. Methionine is the most limiting amino acid but the response to the addition of methionine was very small. Only after supplementation with three amino acids (methionine, tryptophan and threonine) was a substantial growth response obtained. In subsequent experiments, we have found that to improve growth still further, supplementation with a mixture of five other amino acids is required.[10] Thus the obvious procedure for subjects with low protein intakes, who probably need supplements of several amino acids, is to increase the intake of well balanced proteins. Also, it is under conditions of limited protein intake that amino acid imbalances and other adverse effects are most readily demonstrated, and these are most simply avoided by increasing the amount of well balanced protein in the diet.

If the diet is low in only one or two amino acids, supplementation with the missing amino acids will be beneficial, but it is important to know that the amino acids provided are the ones needed. It is also important that the diet be complete in other respects. For example, the type of imbalance shown in Table II can be corrected by the addition of niacin, and it appears that a niacin deficiency

TABLE I

Effect of Gelatin on the Growth of Rats Fed on Diets Containing 6 Per Cent Casein, 0.2 Per Cent DL-Methionine and Dextrin

Dietary Additions	Average Gain (gm./2 wk.)
None	27
0.2% DL-threonine	43
3% gelatin	36
6% gelatin	27
12% gelatin	13
12% gelatin plus 0.2% DL-tryptophan	47

TABLE II

Interrelationships Among Methionine, Threonine and Tryptophan in the Creation of an Amino Acid Imbalance in Rats Fed a Diet Containing 9 Per Cent Casein and Sucrose but Lacking Niacin

Diet Composition (%)				Weight gain (gm./wk.)
Casein	DL-methionine	DL-threonine	DL-tryptophan	
9	...	...	...	10
9	0.3	...	...	12
9	...	0.36	...	10
9	0.3	0.36	...	4
9	0.3	0.36	0.1	20

has been created indirectly by supplementation with threonine. If the diet is a mixed diet, it may be difficult to determine whether all required nutrients are present in the correct amounts. It is one thing to deal with laboratory diets that are highly purified and have been extensively analyzed, and quite another to deal with a mixed diet about which there is very little information.

I would conclude, therefore, that supplementation of the heterogeneous diets of man with one or a few amino acids, particularly in the form of a capsule comparable to vitamin capsules, has no place whatsoever as a general nutritional procedure. It is of no value to the subject receiving sufficient protein to meet his amino acid requirement. It is also unlikely to be of much value to the subject who has an inadequate over-all intake of protein and who probably needs more of most of the amino acids. Also, in such cases, the possibility exists of upsetting the amino acid balance so that some untoward or adverse effect may result.

CONCLUSION

Are we to conclude, then, in spite of the successful use of amino acid supplementation in animal experiments, that amino acid supplementation has no place in human nutrition? This may be unduly pessimistic. We know, for example, that certain foods which contain incomplete proteins can be improved by amino acid supplementation. The nutritive value of many cereal products can be improved by the addition of lysine. The nutritive value of products high in gelatin can be improved by the addition of tryptophan. The nutritive value of many legume proteins can be improved by supplementation with sulfur-containing amino acids. A case can therefore be made for improving the nutritive value of individual foodstuffs to provide *low cost* products with a better amino acid balance. Such products could be used as supplements for low protein diets. It is not possible to generalize about the role of such products in nutrition. It depends upon a great many factors, such as the cost of the products, the state of nutrition of the individual consuming them, and the percentage of the diet made up of such products. Unfortunately, we do not at this time have sufficient information to make a critical appraisal of most of these factors. Even with this information I doubt whether we could generalize. I expect that we would have a series of individual cases that would have to be considered separately. We do know, however, that for the person who is receiving an adequate intake of well balanced protein, there is no need for either amino acid or protein supplementation, and that for the person with a low protein intake the prime need is to increase the over-all intake of well balanced protein.

REFERENCES

1. Wilcock, E. G. and Hopkins, F. G. The importance of individual amino acids in metabolism; observations on the effect of adding tryptophane to a diet in which zein is the sole nitrogeneous constituent. *J. Physiol.*, 35: 88, 1906.
2. Osborne, T. B. and Mendel, L. B. Amino acids in nutrition and growth. *J. Biol. Chem.*, 17: 325, 1914.
3. Flodin, N. W. Amino acids and proteins; their place in human nutrition problems. *J. Agr. Food Chem.*, 1: 222, 1953.
4. Howe, E. E. Amino acid supplementation. *Borden's Rev. Nutrition Res.*, 19: 19, 1958.
5. Elvehjem, C. A. and Krehl, W. A. Dietary interrelationships and imbalance in nutrition. *Borden's Rev. Nutrition Res.*, 16: 69, 1955.
6. Harper, A. E. Balance and imbalance of amino acids. *Ann. New York Acad. Sc.*, 69: 1025, 1958.
7. Salmon, W. D. The significance of amino acid imbalance in nutrition. *Am. J. Clin. Nutrition*, 6: 487, 1958.
8. Evaluation of Protein Nutrition. Publication 711, 1959. National Academy of Sciences—National Research Council.
9. Harper, A. E. and Kumta, U. S. Amino acid balance and protein requirement. *Fed. Proc.*, 18: 1136, 1959.
10. Harper, A. E. Sequence in which the amino acids of casein become limiting for the growth of the rat. *J. Nutrition*, 67: 109, 1959.

Effects of Stress on Animals Fed High Protein Diets

ELIAS HALAC, JR., M.D.*

THERE is no full agreement about the optimum protein intake for human beings of any age, or for animals. This was reflected at a conference held at Princeton,[1] where two eminent nutritionists presented somewhat different views. Elvehjem, then president of the Food and Nutrition Board, was inclined to equate optimum with minimal requirements, judging from the appearance of his experimental animals that protein surfeits were not desirable. King, on the other hand, a member of the same group, argued for a surfeit as providing a margin of safety. It was clear that the data which should settle the argument did not exist.

In 1903 Pflüger[2] proposed the concept of reserve protein, a quantity stored under condition of surfeit to be used in times of deficit. Pflüger did not study this problem himself, but his pupil Seitz did so.[3]

Since then many investigators have contributed their efforts to throw some light on this problem, the most recent one being the excellent work by Ross.[4]

The lack of agreement in which we find ourselves today arises partly from the fact that there is no ideal parameter to be used when interpreting the data. We are faced with the problem of evaluating the effects of a particular protein intake upon the many functions that constitute the animal as a whole. Unfortunately, not all of them vary in a similar fashion. The optimum protein intake to protect against liver disease may not be the one that secures the greatest leeway against the development of vascular and renal degenerative diseases. An optimum protein intake for growth may not be the one that provides the greater life span, and so on.

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Presented at the Ninth International Congress of Paediatrics on July 23, 1959, in Montreal, Canada.

METHODS AND RESULTS

The design of our experiments was guided by our interest in pediatrics. We fed growing rats with two different levels of protein. The control group received a diet that had 27 per cent of its weight as casein, while the other group received a diet that contained 64 per cent as casein. The diets were isocaloric and administered *ad libitum*. The first group will be called N.P.D. (normal protein diet) and the second group, H.P.D. (high protein diet). The rats were started on these two diets when they weighed about 100 gm. After sixty days on these diets they were subjected to stresses that we thought likely to be found in children.

The average weight of the rats in the N.P.D. group was higher than those in the H.P.D. group. Figure 1 shows this difference which became statistically significant at about the forty-fifth day. The curves represent the average of sixty animals in each group.

When a high protein diet is given to an animal, certain changes take place in the body composition. There is a slight increase in the nitrogen content and a decrease in the fat content. The analyses shown in Table 1 were performed by Dr. L. J. Filer[5] according to the technic described by Wallace.[6]

There is no difference in the ash, sodium, potassium or chloride content. It should be noted that the difference in the protein content disappears when a correction is made for the difference in the fat content.

Different tissues differ one from each other in

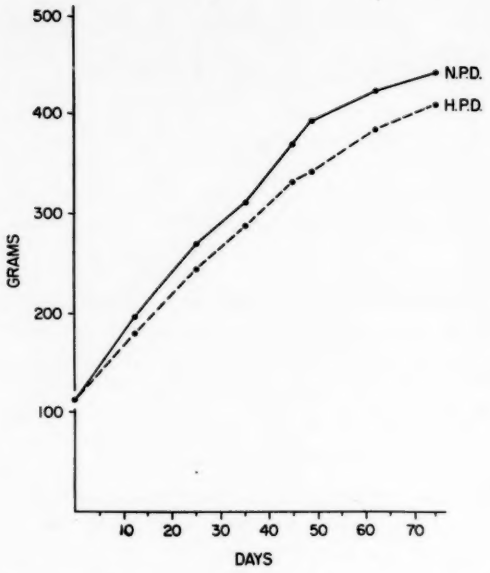

FIG. 1. Weight curves of rats fed a normal diet (N.P.D.) and a high protein (H.P.D.) diet.

their capacity to grow and to "store nitrogen" as the dietary level of protein is raised from low to high levels. Fifteen rats in each group were sacrificed at the end of the sixty-day period and five organs (spleen, liver, adrenals, kidneys and testicles) were weighed. In every instance the weights were higher in the H.P.D. group although the difference in the spleen weight was not significant (Table II).

The more marked and constant differences were found in the adrenal and kidney sizes. It was actually possible to identify the diet fed by glancing at the latter organ.

The first stress was forced exercise. The rats were placed in a cold (5° C.) water bath and allowed to swim until exhausted. The end point is quite easy to determine after a few rats have been observed. Table III shows the result.

In order to correct for the difference in weight a ratio was made of the endurance and weight of each individual animal. The difference remained significant.

In Table IV are shown the results of food starvation upon survival. The longer survival of the rats in the N.P.D. group could be attributed to its higher weight. It was not possible, however, to construct any relationship between weight at the beginning of the starvation and survival.

Tables V and VI show the results of water and water and food starvation. The results of the water starvation test becomes comparable to the latter since within a few days

TABLE I
Carcass Analysis of Whole Unshaven Body

Diet	H_2O (%)	Fat (%)	Protein (%)	Ash (%)	Sodium (%)	Potassium (%)	Chloride (%)
N.P.D.	62.5	14.8	17.7	3.1	18.5	29.9	12.1
H.P.D.	64.9	12.2	18.2	3.1	18.1	29.6	12.3

NOTE: Electrolytes expressed in mEq./100 gm. fat-free dry solids. Values obtained in pooled samples from six rats in each group.

TABLE II
Weight of Organs Expressed as Percentage of Body Weight

Diet	No. of Rats	Body Weight	Liver	Kidney	Adrenal	Testicle	Spleen
N.P.D.	15	478 ±45	2.980 ±0.651	0.516 ±0.084	9.62 ±1.44	0.687 ±0.117	0.143 ±0.032
H.P.D.	15	429 ±44	3.500 ±0.450	0.677 ±0.036	11.98 ±1.83	0.795 ±0.126	0.168 ±0.047

TABLE III
Cold Water (5°c.) Swimming Test

Diet	No. of Rats	Mean Weight (gm.)	Average Endurance	Average Endurance/Weight (sec. gm.$^{-1}$)
N.P.D.	20	438 ± 57	503 ± 124*	1.148 ± 0.340*
H.P.D.	28	393 ± 36	425 ± 44*	1.081 ± 0.272*

* $p < 0.05$.

after the water is withdrawn the animals stop eating.

The next challenge consisted in the administration of whole body radiation with x-rays. Some animals received 700 r and some others 800 r. These doses were applied in fifteen minutes at a distance of 60 cm. at 210 kv. and 20 ma. There was no significant difference in the mortality between the two groups (Table VII).

Table VIII shows the mortality in each group after the intraperitoneal injection of Metrazol.® All the animals had convulsions, and some of them died. The survival rate was higher in the N.P.D. group, but the difference was not significant.

The increase in the nitrogen content of the body that follows high protein diets has been interpreted as a labile fraction that could function as a store, and therefore useful in times of deficit.[7] To test this hypothesis twenty-nine rats in the H.P.D. group and nineteen rats in the N.P.D. group were placed on a protein-free diet after being fed for eighty days with their respective diets. Six rats in each group were sacrificed during the course of the

TABLE IV
Food Starvation

Diet	No. of Rats	Initial Weight (gm.)	Final Weight (gm.)	Survival* (days)
N.P.D.	24	402 ± 41	208 ± 31	27±9
H.P.D.	23	377 ± 35	216 ± 15	21±4

* $p < 0.05$

TABLE V
Water Starvation

Diet	No of Rats	Initial Weight (gm.)	Final Weight (gm.)	Survival* (days)
N.P.D.	20	436 ± 38	176 ± 19	31 ± 5
H.P.D.	26	382 ± 41	183 ± 28	26 ± 6

* $p < 0.05$.

TABLE VI
Water and Food Starvation

Diet	No. of Rats	Initial Weight (gm.)	Final Weight (gm.)	Survival* (days)
N.P.D.	29	357 ± 33	159 ± 15	24 ± 4
H.P.D.	30	329 ± 39	157 ± 19	20 ± 4

* $p < 0.05$

TABLE VII
X-Ray Stress

Diet	No. of Rats	Dose (r)	Mean Weight (gm.)	Mortality*
N.P.D.	20	700	446 ± 41	3
H.P.D.	20	700	491 ± 67	3
N.P.D.	15	800	549 ± 67	4
H.P.D.	15	800	468 ± 60	6

* Animals that died during the seven days following radiation therapy.

TABLE VIII
Metrazol Injection

Diet	No. of Rats	Dose (mg./kg.)	Weight (gm.)	Mortality*
N.P.D.	10	50	420 ± 38	4
H.P.D.	10	50	401 ± 28	6
N.P.D.	20	60	435 ± 31	15
H.P.D.	20	60	398 ± 39	17

* $p < 0.7$.

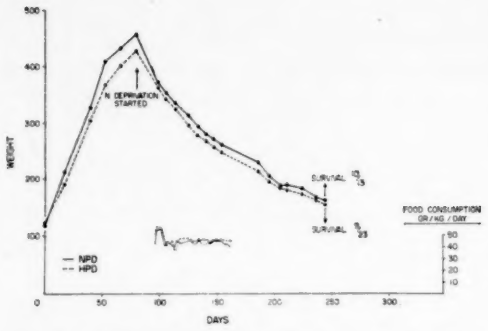

FIG. 2. Effect of diet on survival with protein-free regimen.

experiment for body analysis; therefore only twenty-three rats in the H.P.D. and thirteen rats in the N.P.D. are accounted for mortality purposes.

Figure 2 shows the weight curve of the two groups. The ascending part of the curves show the difference present in all the groups. Immediately after the protein starvation was started both weight curves went down. The rate of decrease was similar. The two lower curves show the food intake by both groups, there being no significant difference between them.

The experiment was called off 169 days after the protein-free diet was started. At this point nine rats in the H.P.D. group and ten rats in the N.P.D. group remained alive, or a mortality rate in the H.P.D. group of 60 per cent against 23 per cent in the control group. These results do not lend any support to the idea that an increase in the nitrogen intake may protect against future deprivation.

These results are valid for rats at the two protein levels used. They cannot be transposed to man or other species at present. The tests were randomly chosen, and it is possible that some others might have given different results. Life span and intellectual capacity are two of the most important aspects of human life. We have not approached the study of these two problems. Other investigators have found that restriction of calories or of protein leads to prolongation of life.[1,8] We do believe that a great deal of work and critical analysis are necessary in this field, in animals and, as far as it can go, in man. Long-term studies are needed as much as or even more than short-term studies. Different kinds of proteins at different levels should be tried. In the meantime, we cannot confirm that with respect to high protein foods, more is necessarily better.

REFERENCES

1. Human protein requirements and their fulfillment in practice. In: Proceedings of a Conference in Princeton, U. S., 1955. Edited by Waterlow, J. C. and Stephen, J. M. L. New York, 1957. F.A.O., W.H.O. and Josiah Macy, Jr. Foundation.
2. PFLÜGER, E. Glykogen. *Arch. für die gesamte Physiologie*, 96: 1, 1903.
3. SEITZ, W. Die Leber als Vorrathskammer für Eiweisstoffe. *Arch. für die gesamte Physiologie*, 111: 309, 1906.
4. ROSS, M. H. Protein, calories and life expectancy. *Federation Proc.*, 18: 1190, 1959.
5. FILER, L. J. Personal communication.
6. WALLACE, W. B., WEIL, W., TAYLOR, A. Ciba Foundation Colloquia in Ageing, vol. 4, Water and Electrolyte Metabolism in Relation to Age and Sex, p. 110, 1958.
7. ALLISON, J. B. Biological evaluation of proteins. *Phys. Rev.*, 35: 664, 1955.
8. MCCAY, C. M., DILLEY, W. E. and CROWELL, M. F. Growth rates of brook trout reared upon purified rations, upon dry skim milk diets and upon feed combinations of cereal grains. *J. Nutrition*, 1: 233, 1929.

DISCUSSION

DR. L. J. FILER, JR. (*Columbus, Ohio*): We have made a series of similar observations on eight week old pigs.* These animals were raised from age three days on either of two diets: one high in protein, low in fat; the other low in protein, high in fat. At fifty-six days of age the animals were subjected to stress either in the form of caloric and water deprivation (stress A), water deprivation with calories supplied (stress B) or caloric deprivation with water provided (stress C).

Table IX relates survival under stress to body composition. From carcass analysis it is apparent that the low protein-high fat diet produced a carcass of approximately 35 per cent fat in contrast to the carcass of the high protein-low fat fed animal with approximately 16 per cent of his carcass as fat. The water content of the carcass under these circumstances reflects an inverse relationship to fat content.

When these animals were stressed by deprivation of food and water (stress A) the fatter animals survived an average of twenty-one days. The leaner animals

* BAUR, L. S. and FILER, L. J., JR. Influence of body composition of weanling pigs on survival under stress. *J. Nutrition*, 69: 128, 1959.

TABLE IX

Relationship Between Diet, Body Composition and Survival Under Stress

Diet	Body Composition (%)		Days Survived (average)		
	H_2O	Fat	Stress A	Stress B	Stress C
Low protein-high fat	49.9	35.2	21 (5) 19–22*	15.5 (2) 15–16	89 (3) 84–93
High protein-low fat	62.8	16.7	28 (5) 25–31	16 (2) 16	36 (4) 34–40

NOTE: Figures in parentheses represent number of pigs per group.
* Range of days survived.

TABLE X

Relationship Between Diet, Body Composition and Survival Under Stress

Diet	Body Composition (%)		Days Survived (average)		
	H_2O	Fat	Stress A	Stress B	Stress C
Low protein-high fat	51.3	32.6	29 (4) 24–32*	23 (2) 23–24	85 (4) 73–94
High protein-high fat	53.8	29.5	23 (4) 18–28	23 (4) 18–27	71 (4) 62–85

NOTE: Figures in parentheses represent the number of pigs per group.
* Range of days survived.

survived an average of twenty-eight days. We interpret this difference in survival to be due to the fact that the leaner animals had a higher content of body water.

When these eight week old pigs were fed whole powdered milk and no water (stress B), survival time was markedly decreased for both groups. It was observed that the pigs ate some whole powdered milk for ten of the sixteen days they survived.

Those pigs that had access to water without food (stress C) survived for longer periods than those subjected to stress A, but in reverse relationship to prior diet. The fatter pigs survived an average of eighty-nine days. The leaner group of pigs had an average survival time of thirty-six days.

Since this initial study contrasted the survival times under stress of pigs fed diets differing in protein content as well as in body composition, an additional experiment was run in which animals were fed either a low protein-high fat diet or a high protein-high fat diet.* These diets were designed to produce animals of comparable carcass composition, i.e., a carcass with a water content approximating 50 per cent and a fat content approximating 30 per cent (Table x). Under the conditions of stress A those animals reared on a low protein-high fat diet survived twenty-nine days, in contrast to twenty-three days for the pigs fed a high protein-high fat diet. These findings are comparable to those observed for the rat by Doctor Halac.

Feeding the whole powdered milk without water (stress B) reduced the survival time of the animals fed the low protein-high fat diet from twenty-nine days (on stress A) to twenty-three days. This stress was without apparent effect on survival of the animals previously reared on a high protein-high fat diet.

When pigs of comparable body composition were permitted access to water without calories (stress C), those that had been fed the low protein-high fat diet survived for a longer period of time, eighty-five days in contrast to seventy-one days. The range of survival times, however, was so great that the difference was not statistically significant.

Due to the ease with which one can modify by dietary means the proportions of fat and water in the pig carcass, this animal offers some advantage in studying the relationship between stress and body composition. Such alterations in body composition are more difficult to achieve in the rat and dog.

DR. L. E. HOLT, JR. (*New York, New York*): I would like to ask Dr. Harper whether he thinks lysine supplementation of foods is desirable for the American public at the present time.

DR. A. E. HARPER (*Madison, Wisconsin*): I think it is unnecessary for the American public as a whole. If we take the average figure for the amount of protein used in the United States it is close to 100 gm. of protein a day. This should supply well above the requirement.

In this regard I was interested to see the abstract of a paper to be presented by Kaye, Valyasevi and Barness on "Evaluation of Cereal Proteins as a Source of Nitrogen in the Growing Infant." According to their abstract they have been able to maintain youngsters, between five and seventeen months of age, in positive nitrogen balance, with wheat proteins alone.

DR. KURT SCHREIER (*Heidelberg, Germany*): To underline Dr. Harper's remarks about supplementation of diets with normal protein content, I should like to tell you that it is possible to induce a more or less generalized hyperaminoaciduria by giving one single amino acid. For instance, we gave 100 mg. lysine per kg. of body weight to infants; in several we found a high excretion of arginine, threonine, glutamic acid, and so on, in addition to the lysine. Therefore, I believe that it may be quite a valuable test for the detection of an imbalance, as Dr. Harper called it, in the food, especially to find out whether it is meaningful to add one single amino acid to a special baby diet.

* FILER, L. J., JR., BAUR, L. S. and REZABEK, H. Influence of protein and fat content of diet on the body composition of piglets. *Pediatrics* 25: 242, 1960.

DR. HARPER: We have not carried out such work ourselves. I am interested to hear about it and should like to make similar studies on experimental animals.

However, we have measured the nitrogenous components of the blood in animals fed on diets in which amino acid imbalances have been created, and found that the concentration of urea in the blood rises.

DR. GILBERT B. FORBES (*Rochester, New York*): Dr. Hegsted, how much do we really know about the protein requirement of human beings, particularly infants and children?

DR. D. MARK HEGSTED (*Boston, Massachusetts*): We know something but not very much. The only comment I would like to make is that I think the evidence from the various sources as to protein requirements ought to be consistent with some thesis or hypothesis. If the evidence derived from different sources is not consistent, then obviously something is wrong either with the data or with our interpretation of it. Most of the data, at least the way I interpret them, are consistent with the theoretic approach to minimum protein requirements.* This approach leads you to believe that in the young infant breast milk supplies about the minimum requirement of protein, and then the protein requirement falls very rapidly with the decreasing rate of growth. I think the data on balance studies have been misinterpreted to indicate requirements higher than they actually are.

DR. JEAN MAYER (*Boston, Massachusetts*): The one comment I would like to make is that because of the context in which *we* live, we tend to think of diet as a fairly stable entity. I think it is well worth remembering that there are many parts of the world—and Dr. Cicely Williams would bear me out on this—where food intake is essentially seasonal. The interpretation of long-range significance of the proportion of proteins to calories, the effect of high protein diets and the whole question of the possible protective effects of overnutrition are quite different when you operate in a context of seasonal food intake, as contrasted to a situation in which the food intake is steady.

For example, in Western societies, where we eat regularly so many meals a day, there is no question but that excessive stores of calories, that is obesity, is a bad thing: its disadvantages, from the point of view of degenerative diseases, are quite obvious. On the other hand, there are situations, when the food intake fails as it does regularly every year in northern Ghana where I was last winter, in which a certain amount of storage of excess calories in the form of fat is a good thing. It is easy to demonstrate that under starvation conditions obese animals survive longer than nonobese animals.

There are other aspects in regard to the interrelationship of calories and proteins which I think are unclear at the present time, and in which many of our present ideas may prove to be too simple. For instance, we used to think that carbohydrates always spared protein so that if we did not receive enough protein we would be better off if at least we had enough or more than enough carbohydrate. Actually the evidence from studies of marasmus and kwashiorkor shows that the problem is much more complicated. It is by no means certain that it is always a good idea to have enough or more than enough carbohydrate when the diet is deficient in protein. Such an individual might be better off with not enough of each. The moment we stop thinking in the context of short-term animal experiments or the context of food habits as we know them in rich Western countries, we find that many unforeseen and at present unexplained complexities appear as regards the effects of diet in children.

DR. FORBES: Two of the papers presented were accompanied by illustrations showing the growth rate of animals. Does anyone know how fast a human infant should grow or what the optimum growth rate is? If we are going to use growth as a criterion of adequacy, we are going to have to define optimum growth as well as optimum nutrition.

Dr. Garn is one of the few people who has actually made a long-term study of the growth of children.

DR. STANLEY M. GARN (*Yellow Springs, Ohio*): I do not know how fast they should grow. Optimum growth rate probably depends on the situation. You see, if we were growing children for culinary purposes, as Dean Swift suggested, the optimum growth rate of course would be that which gave the most child for the least feed.

We have accomplished this very well in animal husbandry where we breed animals for maximum feed utilization. In our own studies in which we followed the growth of children, some of them for a period of thirty years, there is clear evidence that, after the first year and through adolescence, the amount of stored fat is consistently correlated with body size, with the rate of growth and with the age at sexual and osseous maturity. The correlation is about 0.35 throughout that time period.†

During the first year of life, however, the amount of stored fat is peculiarly unrelated to the rate of growth, bone development and so on.

Up to the level of clinical obesity, it is possible to alter the rate of growth and the age of maturation by caloric manipulation. Whether this is good or bad, however, depends on what you are trying to do with the children, whether it is really true that the child's optimum growth rate is his *maximum* growth rate.

DR. NEVIN S. SCRIMSHAW (*Guatemala, Central America*): Dr. Mayer showed how data that pertain to undernutrition can be pertinent to a symposium on overnutrition when he mentioned that a specific deficiency seems to be much less harmful if it is balanced with deficiencies of other essential nutrients. The

* HEGSTED, D. M. *J. Am. Diet A.*, 33:225, 1957.

† GARN, S. M. and HASKELL, J. A. Fat and growth during childhood. *Science*, 130:1711, 1959; *Am. J. Dis. Child.*, 99:746, 1960.

example to which he referred was marasmus, which is essentially a form of starvation. It is noteworthy that in this condition the enzyme changes, skin lesions, cyclic changes and tissue changes of the severe protein malnutrition of kwashiorkor simply do not appear. They appear only when, for some reason or another, there is a disproportion between calories and protein, and then they may appear relatively suddenly. This greater effect of an imbalance of nutrients is a very general principle.

For example, you might think that there could be no possible harm in distributing skimmed milk in an area in which people are protein deficient, but there is pretty good indication that distributing skimmed milk in Indonesia increased the amount of xerophthalmia, keratomalacia and blindness because it accentuated the deficiency of vitamin A. As a principle, adding a relative excess of almost any nutrient, whether vitamin, amino acid or intact protein, when others are deficient, may make the situation worse. This phenomenon certainly fits into the context of this discussion.

Even growth failure may be a fortunate adaptation to lack of sufficient nutrients for growth. If growth is forced in a situation, by suddenly making protein and calories available, a pre-existing vitamin deficiency, not corrected in the dietary change, may be exacerbated.

DR. CICELY WILLIAMS (*London, England*): The variations in the quantity and in the nature of the diet in certain areas do not only depend on seasonal availability, but may also depend on social demands. Some communities consume an inadequate diet for weeks or months, but on the celebration of a wedding or some other festivity they will eat till they vomit, and then start eating again. The calculation of the total amount of food consumed, therefore, may have very litle relation to its nutritional value.

The question of habituation or adaptation to food introduces yet another factor. Adults and young people can adapt themselves to changes in the type of diet and to timing, but for children and old people the process of adaptation needs to be gradual. For instance, in an internment camp we were weighing all the women and children every month. The majority of internees were Europeans, accustomed to the ordinary European diet of dairy products, meat, fruit and vegetables with bread and potatoes as the basic carbohydrates. After internment we had rice to eat, and very little besides; most people lost a good deal of weight in consequence. After a time, most people seemed to become habituated to the rice, and even though the diet did not increase, the weights stabilized, and even began to go up. It was easier for the young adults to become adjusted than for the old people.

There were also some Asians in the camp, who were more accustomed to a rice diet, and their weight did not fall as much as that of the Europeans. In fact some of them put on weight from the start.

Before the end of three and one half years many of the elderly people had died. With liberation we again had bread to eat. Bread was socially acceptable, and was indeed associated with emotional joy, but many people seemed to have lost the power to digest bread, and a number suffered with indigestion and could only eat it in small quantities. It seems as if there are two factors in habituation to food, one social or emotional, and the other physiologic. It is this need for physiologic adaptation that makes the weaning period a difficult one.

The third thing I would like to point out is the rarety of allergies in an undernourished population. In most of South East Asia and in Equatorial Africa, there are very few cases of infantile eczema in comparison with the incidence of the disease, for example, in Australia.

We did see occasional cases of asthma, but these often cleared up after treatment for ascariasis. I do not think that the incidence of eczema has much to do with pigmentation, as it occurs in the children of educated colored people in other parts of the world. A heavy load of ascaris is not needed to create nutritional disorders. Some children are socially upset by the presence of one or two round worms.

DR. FORBES: Dr. Prugh, would you care to comment on the role of social factors in nutrition in our society? Is eating getting to be the great American pastime, or is it merely the fact that we have so much food available.

DR. PRUGH: Not being a social scientist, I do not really consider myself qualified to answer that question. All of us are aware that eating has strong social implications in western society and that these have changed somehow with the change in family patterns, in part arising from increasing urbanization. The introduction of television, as one example, has certainly modified eating habits, with not only TV furniture but TV dinners, etc., having been introduced and with children often eating while watching television.

I was extremely interested in the remarks about the question of adaptation to different diets. I do not pretend to know anything about the adaptive aspects of absorption, although the idea is intriguing. From the psychologic point of view, however, it is quite apparent that there are marked differences among children and among adults in the flexibility with which they can adapt behaviorally to new dietary situations, as well as to new situations involving other challenges. For example, some children do very poorly, in a dietary sense, when they go off to camp. Such children may have rather rigid and inflexible personality structures even at the age of eight or nine years, and are unable to adapt easily to new types of food or eating circumstances, as well as to other types of new situations. Other children may be used to eating very large amounts of food, and may have difficulty in cutting down on their intake when they go to camp. The adaptability of the organism obviously has interrelated physiologic, psychologic and interpersonal facets, which may operate in varying balances in response to changes in diet.

DR. W. R. F. COLLIS (*Dublin, Eire*): I have two observations to mention which we made in the concentration camps in 1945 when we had many thousands of people under our care who had been starved. First of all, we observed the starvation syndrome which has been described here. The patients with the starvation syndrome got thinner and thinner, but they did not show the syndrome of acute kwashiorkor.

We also observed that when we gave protein without carbohydrate, a number of the patients died. Our rationale was to push up their amino acid level as quickly as possible by giving protein hydrolysate, in those days admittedly a crude solution.

Our impression was that giving hydrolysate without enough carbohydrate was harmful. On the other hand, by giving glucose only, we tended to increase the edema in some of the cases. This phenomenon may have been the same as has been described here, namely, that an unbalanced carbohydrate diet tends to bring out the kwashiorkor syndrome. The point that I am trying to make is that when you are dealing with starved people, you must be extremely careful to balance the diet when bringing them out of acute starvation. You should bring the diet up in every way—carbohydrate, fat and protein and, of course, the vitamins. I think these observations should not be forgotten.

Atherosclerosis—A Pediatric Nutrition Problem?

RUSSELL L. HOLMAN, M.D.*

We certainly recognize any condition that is responsible for 54 per cent of the deaths in the United States as being a problem. I think it is a pediatric problem; but whether it is a nutritional problem, I am not too certain at the present time. I do think that pediatricians have definite responsibilities if we are ever to make progress in stopping the ravages of this disease. I wish to present to you what we have seen in studying the natural history of this disease, and then take up some of the basic questions with which we need help.

Figure 1 illustrates our concept of the pathogenesis of atherosclerosis. We believe that atherosclerosis develops in a series of definite stages. It starts in infancy as a fatty streak, and continues as a relatively simple fatty streak for the first two decades of life. Without the fatty streak we believe that there would be no second stage or fibrous plaque, which is produced by the laying down of connective tissue about the fat. Fat becomes concentrated at the base of the fibrous plaque, leaving a yellow core of grumous material covered by a cap of connective tissue. Blood vessels grow into the margins of this plaque. In the fourth and later decades of life various complications take place in these fibrous plaques, such as thrombosis, hemorrhage, necrosis, ulceration or accretion, any one of which may encroach upon the lumen of the artery and produce stenosis. If this stenosis develops rapidly in an artery to a vital organ beyond the capacity of collateral circulation, there then develops the fourth stage of atherosclerosis, clinical episodes—myocardial infarct, stroke, gangrene and the like.

I would like to discuss that portion of the process below the clinical horizon and to emphasize the fact that three important stages occur in the arterial wall before clinical disease becomes manifest: fatty streak, fibrous plaque and complication. I also wish to emphasize that different factors may be responsible for each of these stages in the development of atherosclerotic lesions, and that still other factors may be responsible for determining the occurrence of clinical disease.

The methods we have used to study the natural history of atherosclerosis are quite simple.[1,2] They consist of collecting aortas, coronary arteries and cerebral arteries from unselected autopsies on patients of all ages in a large general hospital and in a medicolegal laboratory. We fix these arteries in formalin, stain them in Sudan IV to delineate the intimal lipid, and preserve them in plastic bags. We then estimate the percentage of intimal surface involved by each of these types of atherosclerotic lesions. Figure 2 shows a set of arteries from one patient prepared in this manner. The dark streaks in the specimens are fatty streaks which have been stained with Sudan IV.

Figure 3 shows the results of our study of aortas collected in the New Orleans area from subjects under forty years of age.[1] It was surprising to find that many children under the age of three had fatty streaks in the aorta;

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* Professor of Pathology. Deceased, May 5, 1960. Dr. Henry C. McGill, Jr., very kindly edited Dr. Holman's remarks for publication.

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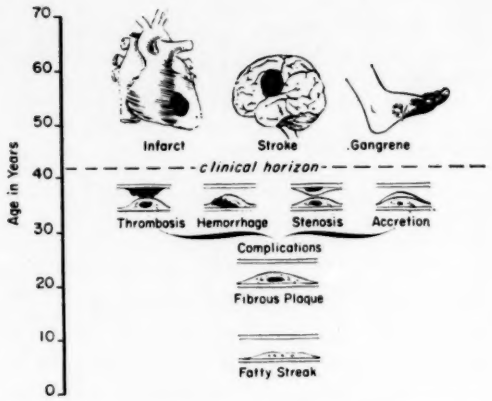

FIG. 1. Concept of pathogenesis of atherosclerotic lesions. The fatty streak is pictured as developing in childhood, being converted into a fibrous plaque in young adulthood. In the thirties and forties, these fibrous plaques undergo changes that produce rapid occlusion of the lumen and thereby precipitate clinical disease in middle life. From HOLMAN, R. L., MCGILL, H. C., JR., STRONG, J. P. and GEER, J. C. *Am. J. Path.*, 34: 209, 1958.[1]

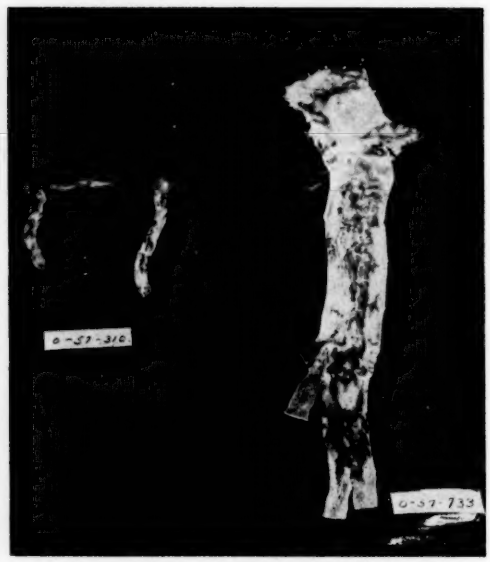

FIG. 2. Aorta and coronary arteries that have been stained with Sudan IV and packaged in transparent plastic bags. Extensive fatty streaks in both specimens show up here as dark areas on the intimal surface. From HOLMAN, R. L., MCGILL, H. C., JR., STRONG, J. P. and GEER, J. C. *Lab. Invest.*, 7: 42, 1958.[2]

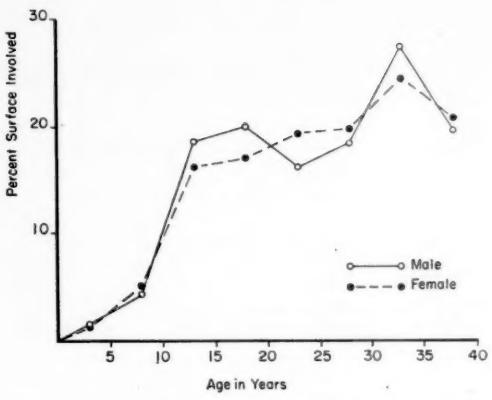

FIG. 3. Average percentage of aortic intimal surface involved with fatty streaks in New Orleans subjects from one to forty years of age.

and furthermore, that every person beyond the age of three years had some degree of fatty streaking. By ten years of age the average percentage of aortic intimal surface involved was approximately 5 per cent. In the second decade, the average percentage of intimal involvement was 20 per cent. Thereafter, the average extent of the fatty streaks remained about the same.

After defining the base line of expectancy for fatty streaks in young persons in the New Orleans area we began to examine specimens from people in other parts of the world, hoping to find some area of the world in which the aorta remains uninvolved. However, specimens collected from Spain, Puerto Rico, Guatemala, Costa Rica,[3] Colombia[4] and even from Bantu in South Africa[5] turned out to have approximately the same frequency and average extent of intimal surface involvement with these same fatty streaks. Some of these groups are shown in Figure 4. This pattern has turned out to be monotonously similar in all parts of the world, regardless of the incidence of clinical heart disease as determined from vital statistics. How are we going to define "normal" if everyone shows these changes?

We have also been concerned with the question of whether the patient's terminal illness has anything to do with the extent of these fatty streaks. As you may know, it

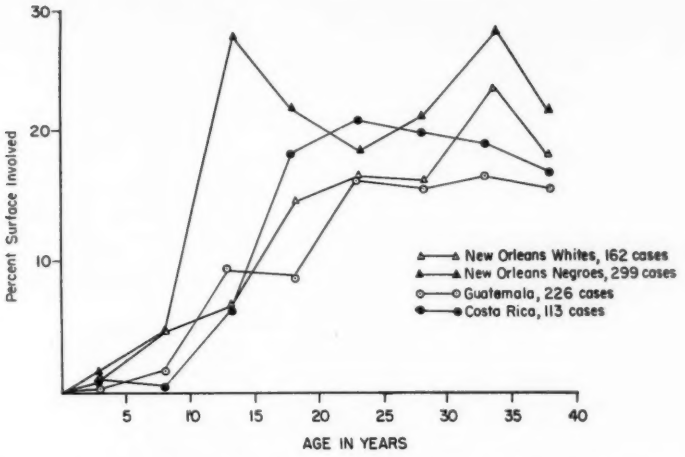

FIG. 4. Comparison of aortic fatty streaks by age and geographic location in subjects from one to forty years of age. From STRONG, J. P., MCGILL, H. C., JR., TEJADA, C. and GEER, J. C. *Am. J. Path.*, 34: 731, 1958.[3]

has been suggested that these lipid deposits are due to infection. Therefore, we compared cases of traumatic death with cases of natural death, most of the latter being due to infection. If anything, the patients involved in accidental deaths showed more involvement, as seen in Figure 5. Since these latter patients represent the best possible sample of the living human population that can be obtained, we conclude that the figures on the extent of aortic fatty streaks in necropsy cases approximates the degree of these lesions in the respective living populations from which they were selected by death.

There is another feature of the results of these studies that has not been demonstrated in the preceeding illustrations, that is, the marked individual variation from one case to another. The differences between two persons of the same age, of the same sex and race, and from the same geographic area may be forty- or fiftyfold. Furthermore, the individual variation in any given geographic area always exceeds the inter-area variation. This is where we need help.

When we go on to the second stage of atherosclerosis, the fibrous plaque, we find some differences that begin to correlate with incidence of clinical disease as indicated by vital statistics. The average white person in New Orleans ends up at age forty with about 15 per cent of the aortic surface covered with fibrous plaques. These fibrous plaques seldom occur before the age of twenty; they develop to a slight degree during the third decade of life; and they grow rapidly during the fourth decade.

In Guatemalans, Costa Ricans and in the Bantu, however, fibrous plaque formation is much less conspicuous. By age forty, aortic fibrous plaques are only one-fifth as extensive in these groups as in the white

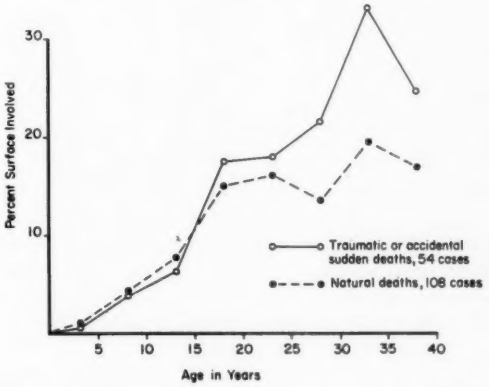

FIG. 5. Comparison of aortic fatty streaks by age and cause of death in white persons in New Orleans. From HOLMAN, R. L., MCGILL, H. C., JR., STRONG, J. P. and GEER, J. C. *Am. J. Path.*, 34: 209, 1958.[1]

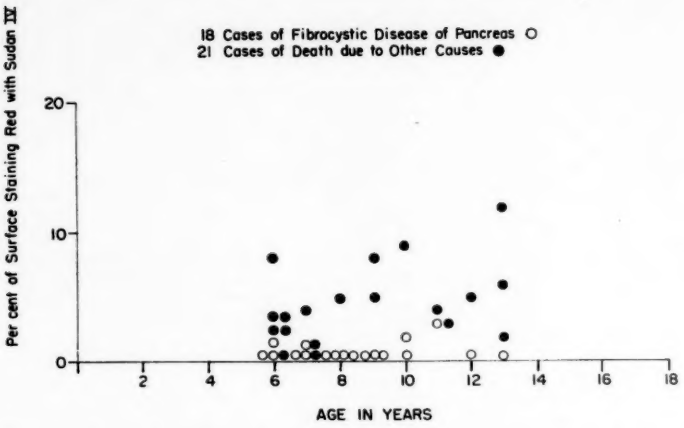

FIG. 6. Comparison of aortic fatty streaks by age and cause of death in eighteen cases of fibrocystic disease of the pancreas and twenty-one cases of death due to other diseases. From HOLMAN, R. L., BLANC, N. A. and ANDERSON, D. *Pediatrics*, 24: 34, 1959.[7]

population of New Orleans, corresponding to the widely recognized differences in frequency of coronary heart disease.[3–5]

We have also conducted similar studies on the coronary and cerebral vessels. We will not go into the details of these results here, but only say that the same process takes place in the other segments of arterial system. It develops in the coronary arteries about twenty years later than in the aorta; and in the cerebral arteries about twenty years later than in the coronary arteries.

What does all this mean? What is the source of this fat? It could arise from increased filtration from the lumen. It could be due to increased local formation, decreased local removal or any combination of these events that would produce a net increase in local lipid content. Studies of the metabolism of intact arteries[6] indicate to us that filtration has been overemphasized and that local formation under hormonal control has been underemphasized. If the pathogenesis of atherosclerosis is to be understood, we believe that the arterial wall should be considered a metabolic factory in its own right.

We have recently described a decreased amount of atherosclerosis associated with one condition, a finding which may yield a clue to the factors influencing the development of these fatty streaks in infancy and childhood.[7] Figure 6 shows a comparison of fatty streaks in eighteen cases of fibrocystic disease of the pancreas with those in twenty-one cases of deaths due to other causes. We do not believe that the differences in body weight are responsible for these differences, for other studies have shown that there was no correlation between body weight and the amount of fatty streaking in the aorta. In fact, obese children may have none and even severely malnourished children may have an average or greater amount.

SUMMARY

To recapitulate the natural history of aortic atherosclerosis, the first two decades of life are taken up with the formation of fatty streaks which we believe are primarily due to local formation. In the second two decades the arterial wall reacts to certain lipids with the proliferation of connective tissue elements. Later complications may precipitate one or more of the well known clinical manifestations.

The pediatric component of the problem is the development of aortic fatty streaks beginning in infancy and accelerating during puberty. Aortic fatty streaks are universal in all parts of the world so far studied and appear to be independent of diet.

An important consideration is the marked individual variation in extent of these lesions, which could be genetic; it does not appear to be ethnic.

Fibrocystic disease of the pancreas is associated with a decreased amount of fatty streaking in the aorta and might be investigated as a possible clue to the etiology and pathogenesis of this lesion.

REFERENCES

1. Holman, R. L., McGill, H. C., Jr., Strong, J. P. and Geer, J. C. The natural history of atherosclerosis. The early aortic lesions as seen in New Orleans in the middle of the 20th century. *Am. J. Path.*, 34: 209, 1958.
2. Holman, R. L., McGill, H. C., Jr., Strong, J. P. and Geer, J. C. Technics for studying atherosclerotic lesions. *Lab. Invest.*, 7: 42, 1958.
3. Strong, J. P., McGill, H. C., Jr., Tejada, C. and Holman, R. L. The natural history of atherosclerosis. Comparison of the early aortic lesions in New Orleans, Guatemala and Costa Rica. *Am. J. Path*, 34: 731, 1958.
4. Restrepo, C. and McGill, H. C., Jr. The early lesions of aortic atherosclerosis in Cali, Colombia. *Arch. Path.*, 67: 618, 1959.
5. Strong, J. P., Wainwright, J. and McGill, H. C., Jr. Atherosclerosis in the Bantu. *Circulation*, 20: 1118, 1959.
6. Strong, J. P., McGill, H. C., Jr. and Nyman, M. A. Deposition of lipid in the calf aorta maintained in vitro. *Circ. Res.*, 5: 294, 1957.
7. Holman, R. L., Blanc, W. A. and Andersen, D. Decreased aortic atherosclerosis in cystic fibrosis of the pancreas. *Pediatrics*, 24: 34, 1959.

Serum Cholesterol Studies in Infants

A Comparison of Infants Fed Breast Milk, Evaporated Milk and Prepared Milk Formulas

JULIUS POMERANZE, M.D.*

THE relationship of lipid metabolism and serum cholesterol levels in atherosclerosis is still not resolved. However, it has been shown in adults that unsaturated fats added to the diet in sufficient proportions will lower serum cholesterol levels.

Man is presumably an atherogenic animal. Dr. Holman has shown that atherogenesis may occur very early in childhood. If the serum cholesterol level is a true barometer of the degree of susceptibility to atherosclerotic changes, then the area of infancy and childhood deserves intensive study. Present day efforts are concerned with reversing the atherosclerotic changes which occur in adults and with averting sequelae. Preventive medicine, however, would be better served if alterations in etiologic factors were attempted during the formative years.

It is quite possible that many nutritional aspects of infancy and childhood play prominent roles in the pathophysiology of adulthood, not only by virtue of habits learned but also through metabolic alterations which are maintained.

Since 1957, Drs. L. B. Slobody, Alta Goalwin and I, as well as other members of our department, have conducted intensive research on the relationship of serum lipid levels to infant feeding procedures. At birth the mean serum cholesterol level is 75 mg. per 100 ml. and rises rapidly during the first four months of life when it approximates adult levels. Infants fed a specially prepared corn oil replacement formula manifest a slower rise and a lesser peak of serum cholesterol.[1,2] The clinical significance of these findings is unclear. It would be unwise to infer a relationship between these laboratory findings and the pathogenesis of aortic and coronary atheromatosis.

Our present study is an extension of previous experimental procedures and includes a comparison of serum cholesterol levels in breast-fed infants, infants fed a typical evaporated milk formula and infants fed an isocalorie formula prepared from milk and containing corn oil as a replacement for butter fat. Four groups of normal infants were evaluated over a sixteen-week period. Group I was comprised of forty-eight infants fed an evaporated milk formula with fruits as the only supplement until the twelfth week of life, after which no dietary restrictions were imposed. In group II, twenty-eight infants received a prepared milk high in unsaturated fats and fruit supplement until the twelfth week after which a free diet was permitted. Six infants in group III were fed similarly but the original diet was maintained for sixteen weeks. Group IV consisted of six breast-fed infants observed for twelve weeks.

Infants in group I manifested the usual rapid rise in serum cholesterol level, with a mean value 187 mg. per 100 ml. at twelve weeks of age. No further increase in serum cholesterol level was produced by supplementation with cereals, vegetables, meat and other dairy

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products at twelve weeks. Infants in group II had a significantly lower mean serum cholesterol level of 127 mg. per 100 ml. Shortly after cereal, meat and vegetable supplementation after twelve weeks, the serum cholesterol level rose to 172 mg. per 100 ml.

This precipitous rise in serum cholesterol level did not occur after the twelfth week in infants in group III who did not receive the supplementary food offered to those in group II. Infants in group IV who were breast fed showed a serum cholesterol pattern remarkably similar to those in group I. There was a rapid rise in serum cholesterol.

REFERENCES

1. Pomeranze, J., Goalwin, A., and Slobody, L. B. Effect of a corn oil-evaporated milk mixture on serum cholesterol levels in infancy. *Am. J. Dis. Child.*, 95: 622, 1958.
2. Pomeranze, J., Goalwin, A., and Slobody, L. B., Influence of diets high in essential fat. (Abstract.) *Am. J. Dis. Child.*, 98: 498, 1959.

DISCUSSION

Dr. Alastair C. Frazer (*Birmingham, England*): I was extremely interested in Dr. Holman's observation on children with pancreatic fibrosis. While I am sure he is right, that the metabolic activity of the arterial wall is a very important matter, it is, of course, interesting that the main change, so far as blood lipid composition is concerned in children with fibrocystic disease, is the almost complete absence of particulate fat. The ordinary alimentary hyperlipemia is commonly absent in children who have no pancreatic enzymes. All patients with fibrocystic disease, however, do not necessarily have complete absence of pancreatic enzymes.

It might be interesting to know whether those who show some changes in the lipid content of the blood vessel wall are those who, in fact, do not have a complete absence of pancreatic enzymes and are, perhaps, showing some abnormalities of lipid metabolism.

Dr. Holman: The best answer I can give to your question is that the majority of the patients with fibrocystic disease which we studied were receiving pancreatin therapy; with this they absorb up to 75 per cent of ingested lipid.

We were concerned at one point with the possibility that chronic infection—which these patients always show—might be an important factor. However, patients with other types of chronic infection do not show such a low incidence of aortic involvement.

To me, an attractive possibility is that the progressive segmental occlusion of the pancreatic ducts in this disease might lead to damming back of lipase and the escape of lipase into the blood, where it might facilitate removal of lipid from the arterial wall. We do not, however, have any direct evidence to support this hypothesis.

Dr. Stanley M. Garn (*Yellow Springs, Ohio*): Dr. Holman, would you comment on sex differences in your data? I remember about ten years ago that Dr. Dock reported an almost male-specific incidence of early plaque information.

Dr. Russell L. Holman (*New Orleans, Louisiana*): At that particular time, Dr. Dock was describing the microscopic intimal thickenings in the coronary arteries in infants. Our studies are on the lipid-rich lesions, studied on the basis of gross appearance of the aorta. With our methods, we found that the aorta of the white female was least involved with fatty streaking, the Negro male most involved, and the Negro female and white male were intermediates. Thus, there is a slight difference in favor of males, but nowhere was this as great as Dr. Dock found in the coronary arteries.

Dr. S. E. Snyderman (*New York, New York*): I would like to add another factor which may influence serum cholesterol levels in infants. In our studies on amino acid requirements of infants we use a complete synthetic diet in which a mixture of eighteen l-amino acids is the source of nitrogen, and corn oil provides the fat. Omission of a single essential amino acid very frequently results in a marked reduction of the cholesterol level, from a control range of 135 to 150 to below 100 mg. per 100 ml. When the missing amino acid is once more included in the diet, the cholesterol immediately returns to normal control levels. These studies have been carried out in infants under four months of age.

Dr. Sarett: I would like to supplement the information that Dr. Pomeranze gave on the serum cholesterol levels of infants. In other unpublished experiments, it has been found that the cholesterol levels are high in breast-fed infants and in those fed evaporated milk diets, in contrast to lower levels found when unsaturated fats are substituted for butter-fat in milk diets.

Dr. Calvin Woodruff (*Nashville, Tennessee*): We have some preliminary observations also on serum cholesterol levels in breast-fed infants and evaporated milk-fed infants. By the age of six weeks, the cholesterol levels in the breast-fed infants are slightly higher than in the infants fed evaporated milk, with average levels of 161 mg. per 100 ml. for breast-fed infants and 154 mg. per 100 ml. for evaporated milk-fed infants. This difference is found only in the female infants.

Dr. Sam Fomon* has a paper in press, using similar feedings and with essentially similar results. In our infants, the dienoic acid (linoleic acid) level in the blood is twice as high in the breast-fed infants as it is in the artificially-fed infants.

It would appear, at least in the six-week age group, that the correlation between low cholesterol levels and high dienoic acid levels which occur in adults may not

* *J. Dis. Child.*, 99: 27, 1960.

exist. The breast-fed infants at six weeks have much higher dienoic acid concentrations than evaporated milk-fed infants but they do not have lower cholesterol concentrations. This brings up the question that Dr. Pomeranze referred to, namely, that in breast-fed infants where there are qualitative and quantitative changes in the fat eaten by the mother, to what extent can one use such infants as the desirable norm?

DR. L. E. HOLT, JR. (*New York, New York*): I would like to put in a word of caution about breast milk fat in this connection. Nobody has called attention to the fact that breast milk fat varies enormously with the diet of the mother. This was pointed out by German pediatricians more than fifty years ago and has been verified by a number of other workers since then.

If one feeds the mother a diet high in unsaturated fat, her milk fat shows this very promptly in a matter of hours.

DR. E. H. AHRENS, JR. (*New York, New York*): Dr. Holman, in regard to fatty streaks you have described an increase in incidence and severity which is directly proportional to age in years, while for fibrous plaques there is a sudden rise in incidence after twenty-five to thirty years of age. Do you not think that this argues aginst the concept that fatty streaks are the precursors of fibrous plaques? What direct evidence can you cite which shows that fibrous plaques are formed from fatty streaks? It seems to me this point is central in the disagreement between your concept of atherogenesis and that of Dr. Duguid and the English school of pathologists.

DR. HOLMAN: I would like to disregard these fatty streaks completely and say they have nothing to do with atherosclerosis. It would simplify the whole problem. But you cannot look at these blood vessels day after day and believe that. All sorts of transitional stages are seen. We have never found a fibrous plaque without a fatty streak. The question hinges on the fate of a fatty streak. Our studies indicate that by age forty, roughly one-third of the fatty streak has disappeared, one-third of it remains status quo, and one-third of it has progressed to a fibrous plaque.

We are acutely aware of the problem you raised, but there is just too much evidence of a real relationship between the fatty streak and the fibrous plaque.

To discuss breifly the second part of your question, namely, the question of fibrin incrustation as the mechanism for fibrous plaque formation: I mentioned that fibrin incrustation was one of the mechanisms by which fatty streak could become a fibrous plaque. We get the impression, however, that most of the transformation of fatty streak to fibrous plaque is due to reactive fibrosis, and I believe that this is the most important process involved.

Clinical Reports

Folic Acid, Vitamin B_6, Pantothenic Acid and Vitamin B_{12} in Human Dietaries

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THE Food and Nutrition Board of the National Research Council[1] has recommended daily dietary allowances for most of the B vitamins. However, there has been insufficient information to permit the setting of levels of intake for folic acid, vitamin B_6, pantothenic acid, and vitamin B_{12}, all of which are involved in human metabolism. There is increasing evidence that they are necessary in the diet of man.

Several types of information are pertinent to assessing adequate or recommended levels of intake of nutrients. These include (1) observations on the occurrence of deficiency in man, (2) results of therapy in clinical syndromes associated with a deficiency, (3) data derived from metabolic studies and induction of experimental deficiency, and (4) quantitative determination of intakes of the nutrient.

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This study was conducted to determine the quantitative intake of folic acid, vitamin B_6, pantothenic acid and vitamin B_{12}. A series of "typical" meals were prepared and analyzed microbiologically for these vitamins. The results obtained provide an estimate of their daily intake by persons in the United States, along with some indication of the day-to-day variability in intake and of variation in cost of the dietary. One stimulus for the study was to ascertain a "reasonable dietary intake level" of these nutrients to serve the Council on Foods and Nutrition as a guide in planning suggested levels of supplementation.[2]

EXPERIMENTAL METHODS

Three sets of diets (adequate high cost, adequate low cost and "poor") were planned and prepared. The adequate high and low cost diets were one week menus designed according to master food plans published by the Bureau of Human Nutrition and Home Economics of the United States Department of Agriculture.[3] The "poor" diets were patterned after menus selected from the recorded diets of pregnant women who participated in the Vanderbilt Cooperative Study of Maternal and Infant Nutrition.[4] They represent the poorest group of diets recorded in the study and were selected from those which supplied an average daily intake of approximately 1,000 calories and 32 gm. of protein. From the weekly diet records, an average day's intake was reproduced. These "poor" diets fail by a considerable margin to meet the Food and Nutrition Board's recommended dietary allowances for protein, calories, thiamine, riboflavin and niacin. Even though these recommended allowances contain a considerable margin of safety, these

diets are so grossly inadequate that, if consumed over a long period of time, they might be expected to lead to weight loss and perhaps other evidence of malnutrition.

All foods were purchased at one local supermarket in order to insure uniform prices. Insofar as possible, fresh meat of superior grade and premium cuts (U. S. Prime), highest quality frozen vegetables and fresh fruits were used in the high cost diets. Lower grades (U. S. Utility) and economy cuts of meat and cheaper grades of canned vegetables and fruits were procured for the low cost and "poor" diets. Source, size, brand, and cost of each item were recorded. Calculations of protein and calorie content, as well as the cost of each set of diets were made. Examples of a week's high cost, low cost and "poor" diets are shown in Tables I, II, and III. Table IV shows the average calculated nutrient content of the three sets of diets, as well as the sources for calculation of the nutrients.

High cost and low cost meals were prepared in the laboratory according to accepted home cooking procedures. For complicated meat or dessert dishes a standard cookbook procedure was followed. The "poor" dishes were cooked in a manner to reproduce as nearly as possible the conditions of home preparation in the region and for the socioeconomic group represented. Preparation was based on the suggestions of persons who took an active part in the Vanderbilt Cooperative Study of Maternal and Infant Nutrition[4] and who were familiar with the cooking methods of persons represented in the study.

Weighed aliquots of individual foods were taken for analysis as representative meals were cooked. If the nature of a food made uniform sampling difficult, it was homogenized prior to taking the sample. Visible fats (such as oleomargarine, butter, and oil) were omitted from the diets in order to simplify analytical work. For analysis, aliquots of all three meals of one day were combined and homogenized and thereby constituted one sample. All samples were quick-frozen and stored in a deep freeze until assayed. Moisture (gravimetric), nitrogen (Kjeldahl method) and crude fat (ether extract) were determined by the standard procedures of the Association of Official Agricultural Chemists.[5] Protein content was calculated as total nitrogen × 6.25.

Folic acid was assayed microbiologically using Streptococcus faecalis (29-21) and the basal medium of the Association of Official Agricultural Chemists modified by the addition of 50 μg. per ml. (double strength media) of methionine.[6] This strain of Streptococcus faecalis has been used successfully in Vanderbilt's laboratory for several years; whereas, both Streptococcus faecalis (ATCC 8043) and Lactobacillus casei have proved less reliable. Chicken pancreas digests of the samples for assay were made according to the method described by Toepfer and his associates.[7] Vitamin B_6 (pyridoxine) was determined with Saccharomyces carlsbergensis (ATCC 4228) using the medium and extraction procedure of Atkin and co-workers.[8] Lactobacillus arabinosus (ATCC 8014) was employed for the assay of pantothenic acid. Difficulties were encountered with this procedure when commercial media were used but a medium devised in Vanderbilt's laboratory proved satisfactory. It is similar to the one used by Hoag and others[9] but omits the acid-hydrolyzed casein. Preparation of samples for the assay of "free" and "total" pantothenate was made according to the enzymatic method of Zook and associates.[10] This method for "total" pantothenate yields values comparable to those obtained by animal bioassay technic.

L. leichmannii (ATCC 7830) was employed for the assay of vitamin B_{12}, using Difco dehydrated U.S.P. media. Duplicate 2 gm. aliquots of the sample were weighed in tared beakers. To these were added 4 ml. of pancreatin (2 mg. per ml. in phosphate buffer pH 6.7, 0.1M) and enough water to make a volume of 10 ml. After twenty-four hours of incubation at 37°c. in a water bath, one of the duplicates was diluted with 4 ml. of water and the other with 4 ml. of 0.5 N sodium hydroxide. Both samples were heated in a boiling water bath for thirty minutes to destroy the vitamin B_{12} in the tube to which alkali was added, neutralized to pH 6.7, and diluted appropriately for the microbiologic assay.

RESULTS AND COMMENTS

Results of the analysis of the diets are given in Table IV and are compared to calculated values when possible. The average daily retail cost per person for each type of diet, based on price levels existing in the winter of 1957, was: high cost, $2.44; low cost, $0.54; and poor, $0.34.

Both high and low cost diets were considered adequate by current standards since they contained quantities of the common nutrients that usually were well in excess of the Recommended Dietary Allowances of the Food and Nutrition Board. However, the poor diet only met the allowance for vitamin A. Calculated and analytical values for protein were in excellent agreement but fat values by analysis were routinely 15 to 20 per cent lower than those calcu-

TABLE I

TABLE 1
One Week's Menus of High Cost Diets

Day						
1	2	3	4	5	6	7
Breakfast						
Grapefruit with cherry Scrambled eggs Bacon Muffins Jelly Butter Milk Coffee	Tangerine juice Fried egg Country sliced ham Biscuits Preserves Butter Milk Coffee	Orange juice Pancakes with syrup Canadian bacon Coffee Milk	Grapefruit juice Cornflakes with milk Scrambled eggs Sausage Jelly Muffins Butter Coffee	Grapefruit with cherry Maltomeal with milk Poached egg Toast Butter Jelly Coffee	Orange juice Waffles with syrup Link sausage Coffee Milk	Tangerine juice French toast with syrup Canadian bacon Coffee Milk
Lunch						
Cream of asparagus soup with crackers Tuna salad sandwich with relishes Potato chips Lemon meringue pie with graham cracker crust Coffee	Pizza pie (pepperoni) Italian salad (lettuce, cucumber, egg, tomatoes, green pepper, spinach) Strawberry shortcake Milk	Mixed grill (lamb chop, bacon, sweetbread, tomatoes, pineapple, banana) Biscuits Butter Tapioca pudding with almonds Milk	Shrimp salad bowl (eggs, shrimps, celery, pickles) Potato chips Cherry pie ala mode Milk	Oyster stew Toasted cheese and bacon sandwich Relishes White cake with raisin and almond garnish Milk	Chef's salad dinner plate (cheese, bacon, egg, celery, green pepper, carrots and lettuce) Ritz® crackers Orange chiffon cake Milk	Turkey pot pie Tomatoes and cucumber salad Apple pie with cheese Milk Coffee
Dinner						
Shrimp hors d'oeuvres Broiled T-bone steak French fries Buttered green peas* with mushrooms Tossed salad Hot rolls Butter Cherry vanilla ice cream Coffee	Stuffed celery Roast fillet of beef Mashed potatoes Buttered green beans Fresh fruit salad Angel food cake with fudge sauce Coffee	Cocktail anchovies with Ritz crackers Fresh pork tenderloin Mashed sweet potatoes with marshmallow Broccoli* Pear and cheese salad Orange sherbet with chocolate chip cookies Coffee	V-8 juice cocktail Baked ham with fruit sauce Mashed potatoes Green peas* Pineapple, cabbage, and marshmallow salad Rolls Butter Pecan fudge devil's food cake Coffee	Potato snappies Liver and onions Paprika potatoes Asparagus* Rolls Butter Cole slaw Vanilla macaroon cupcake Coffee	Chilled fruit cocktail Seafood platter (shrimps, scallops, oysters) French fries Carrots* Head lettuce salad Hot rolls Butter Strawberry Sundae Coffee	Carrot and celery curls Fried chicken Mashed potatoes Buttered broccoli* Apple, grape and celery salad Hot rolls Butter Pumpkin pie with whipped cream Coffee

* Frozen.

TABLE II
One Week's Menus of Low Cost Diets

Day						
1	2	3	4	5	6	7
Breakfast						
Orange juice* Pancakes with syrup Margarine Coffee Milk	Peaches* Boiled egg Toast Margarine Milk Coffee	Grapefruit juice* Maltomeal with milk Toast Margarine Coffee	Orange juice* French toast with syrup Milk Coffee	Tomato juice* Shredded wheat with milk Toast Jelly Margarine Coffee	Orange juice* Cream of Wheat Toast Margarine Milk Coffee	Grapefruit juice* Poached egg Bacon Toast Milk Coffee
Lunch						
Boston baked beans Mixed raw vegetable salad (spinach, celery, carrots) Bread Margarine Grapes Coffee	Egg noodles and tuna Green cabbage Pineapple salad Crackers Margarine Milk	Chili con carne Banana log salad Angel food cake Milk	Broiled sausage and pineapple Mixed green salad (mustard greens, celery leaves, green cabbage) Bread Margarine Pears* Coffee	Broiled fish with lemon Baked potatoes Buttered beets Chopped lettuce salad Rolls Margarine Pears* Coffee	Macaroni creole with ground meat Turnip greens Muffins Margarine Pears* Coffee	Baked pinto beans with cheese Buttered potatoes Fresh green beans Tomatoes* Peaches* Milk
Dinner						
Broiled pork liver Buttered potatoes Carrots Bread Margarine Peaches* Milk	Black bean soup Grilled cheese sandwich Celery and carrot sticks Chocolate chip cookies Coffee	Fresh vegetable salad bowl (spinach, cabbage, eggs, cheese) Crackers Orange cup cake Peaches* Coffee	Baked beans and bacon on toast Boiled spinach with lemon Crackers Apple ring salad Milk	Meatloaf with catsup Buttered potatoes Green peas* Carrot and celery sticks Apple Milk	Potato and onion soup Plain omelet Turnip greens Bread Margarine Vanilla Macaroon cupcake Milk	Bean soup Hamburger with lettuce and onion Apple Milk

* Canned.

TABLE III
One Week's Menus of Poor Diets

Day						
1	2	3	4	5	6	7
Breakfast						
Fried egg Bacon Toast	Fried egg Bacon Toast	Biscuits Oats with milk and sugar	Oats with milk and sugar Biscuits	Orange Cornflakes Toast Milk	Oats Toast	Biscuits Oats with milk and sugar Jelly
Lunch						
Summer squash Fried potatoes Lettuce Green onions Cornbread Iced tea with sugar	Bologna sandwich Lemonade with sugar	Fried potatoes Spinach Iced tea and sugar	Irish potatoes Cornbread Iced tea	White beans Cornbread Fried corn Milk	Tomato soup Cabbage Fresh green beans Cornbread	Tomato soup Crackers Banana
Dinner						
Fried corn Fried potatoes Lettuce Green onions Cornbread	Fried corn Green beans Squash Green onions Cornbread	Dried beans Irish potatoes Cornbread	Turnip greens Coleslaw White beans Cornbread	White beans Cornbread Turnip greens	Tomato soup Crackers Apple Lettuce	Biscuits Milk Bread Jelly Apple

TABLE IV

Average Nutrient Content of High Cost, Low Cost "Adequate" and Poor Diets as Calculated from Food Composition Tables* and as Determined by Microbiologic Assays†

Nutrient per Day	Diet								
	High Cost			Low Cost			"Poor"		
	Calculated	Analyzed	Analyzed Range	Calculated	Analyzed	Analyzed Range	Calculated	Analyzed	Analyzed Range
Calories	3,013	...	...	2,439	...	...	1,117	...	...
Protein (N × 6.25) (gm.)	126	130	98–155	112	116	74–150	32	31	23–46
Fat (gm.)	169	140	120–174	95	73	31–118	34	29	10–46
Vitamin A (I.U.)	13,076	...	...	17,303	...	...	6,277	...	...
Vitamin C (mg.)	147	...	...	134	...	...	55	...	...
Thiamine (mg.)	1.9	...	...	1.4	...	...	0.9	...	...
Riboflavin (mg.)	3.7	...	...	3.1	...	...	1.1	...	...
Niacin (mg.)	22.0	...	...	16.9	...	...	6.4	...	...
Calcium (gm.)	1.5	...	...	1.5	...	...	0.6	...	...
Phosphorus (gm.)	1.9	...	...	1.8	...	...	0.7	...	...
Iron (mg.)	22.7	...	...	18.9	...	...	10.0	...	...
PGA "free" (μg.)	33.3	65.2	22.0–172.0	43.4	67.9	30.0–153.7	11.4	15.2	8.0–21.0
PGA "total" (μg.)	120.4	193.4	160.0–346.0	117.0	157.4	104.5–309.5	30.8	47.3	26.8–64.7
Vitamin B_6 (mg.)	...	2.0	1.1–3.2	...	2.7	1.6–3.6	...	1.0	0.7–1.4
Pantothenic acid "free" (mg.)	6.7	8.0	5.3–11.7	4.9	6.6	4.0–12.1	2.2	1.9	1.3–2.5
Pantothenic acid "total" (mg.)	11.0	16.3	13.3–19.2	8.9	14.2	9.9–20.5	4.1	6.0	5.2–7.2
Vitamin B_{12} (μg.)	...	31.6	4.1–85.5	...	16.0	1.2–75.6	...	2.7	1.1–8.1

* Calculated PGA values are based on U. S. Dept. of Agriculture Handbook No. 29, 1951. Calculated pentothenic acid values are based on U. S. Dept. of Agriculture Handbook No. 97, 1956. Other calculated nutrients are based on U. S. Dept. of Agriculture Handbook No. 8, 1950.

† All values were obtained by averaging results from two to four determinations.

lated. A similar discrepancy has been noted in other recent studies. In our study this was not attributable to the omission of visible fat as this was taken into consideration in the calculations. The values apparently are erroneously low due to incomplete extraction under the conditions employed. Mild acid hydrolysis prior to extraction probably would result in more complete extraction.[11] Sufficient data were not available to permit calculation of the pyridoxine and vitamin B_{12} contents of the diets. Available data on the folic acid and pantothenic acid contents of foods are incomplete so that the "calculated values" for these vitamins could not include all the foods in the diet. These "calculated values" are lower than the actual or analyzed values.

The high cost diet furnished from 160 to 346 μg. of "total" folic acid activity daily (mean = 193) and the low cost diet furnished from 105 to 310 μg. of "total" folic acid daily (mean = 157). The "poor" diet contained considerably less folic acid and provided a daily "total" intake of only 27 to 65 μg. As might be expected, the daily intake of "free" folic acid activity was considerably less for all diets.

The assay of selected samples for the three types of diets with Str. faecalis (ATCC 8043) yielded values higher than those found with Str. faecalis (29-21) (Table v). Although early studies demonstrated that these two organisms gave similar values on certain foods, it now is apparent that they do not respond in an identical manner to certain folic acid derivatives. For example, N^{10} formyl-folic acid, Ca leucovorin, anhydro-leucovorin, anhydro-leucovorin A, and pteroic acid have a greater activity for Str. faecalis (8043) than for Str. faecalis (29-21). However, it is estimated that the slight differences in response to these compounds

TABLE V
Folic Acid Content of Selected Diets as Assayed with Str. faecalis (ATCC 8043) and Str. faecalis (29-21)

Diets	"Total" Folic Acid (μcg./day)		"Free" Folic Acid (μcg./day)	
	Str. faecalis (ATCC 8043)	Str. faecalis (29-21)	Str. faecalis (ATCC 8043)	Str. faecalis (29-21)
High cost No. 3..	389 9	159 9	127 4	29.7
Low cost No. 6..	239.5	111.8	93.4	35.4
"Poor" No. 1....	161.2	64.7	68.8	21.0
"Poor" No. 2....	102.2	53.1	26.9	13.1

should not raise the values obtained with Str. faecalis (8043) by more than 10 per cent—an increase considerably less than that actually observed. This leads to the obvious conclusion that Str. faecalis (8043) responds quantitatively and/or qualitatively to a greater variety of folic compounds than does Str. faecalis (29-21). The nature of these substances is not known. It is of interest that both the "total" and "free" folic acid content of the diets as calculated from food tables are within the limits found by assay with Str. faecalis (29-21), despite the fact that the values in the tables are presumably based on results obtained using Str. faecalis (8043).

Of the known forms of folic acid, monoglutamate, diglutamate, triglutamate, and heptaglutamate all have been effective in the treatment of sprue in man, but the minimal quantities of these conjugates that will produce a hematologic response in this disease apparently have not been determined.[12] Woodruff, Peterson and Darby[13] reported that infants with megaloblastic anemia responded to the oral administration of 200 and 500 μg. daily of folic acid. Jones and Darby (unpublished) observed that the parenteral administration of 100 μg. of folic acid daily resulted in a reticulocyte response, but unsatisfactory erythropoiesis, in an adult with pernicious anemia. Although it is obvious that requirements cannot be defined precisely on the basis of available information, it is reasonable to assume that the total daily folic acid requirement of the normal adult does not exceed 0.2 mg. of folic acid activity as measured by Str. faecalis (29-21) or 0.4 mg. of activity as estimated by Str. faecalis (8043). These levels of intake may be considerably more than adequate since they were found in diets that were luxurious by current dietary standards. Williams[14] suggested that 1 mg. of folic acid represents a safe level for daily intake, but this figure obviously is high if assays are made with Str. faecalis.

The vitamin B_6 activity of the adequate diets studied ranged from 1.1 to 3.2 mg. per day, averaging 2 and 2.7 mg., respectively, for the high cost and low cost rations. The average quantity supplied by the poor diets was 1 mg. daily, the lowest amount was 0.7 mg.

This estimated daily intake on adequate diets of around 2 mg. is comparable to the 1 to 1.5 mg. noted by Vilter[15] as a result of analyses of regular hospital diets. Williams[14] estimated 1.5 mg. daily to be the human requirement of vitamin B_6.

Even though Snyderman and others[16] found that a daily oral dose of 1 mg. of pyridoxine was sufficient to prevent the convulsions that characterize a deficiency of this nutrient in the infant, some evidence shows that the requirement of certain infants may be higher. For example, Bessey and others[17] reported that two of nine infants studied required daily intakes of 2 and 5 mg., respectively, to control convulsions. From this and other evidence, Hunt[18] has suggested that genetic metabolic defects of vitamin B_6 metabolism may exist which are manifested by abnormally high vitamin B_6 requirements. However, this hypothesis is purely speculative and more detailed clinical and biochemical evidence is required before it can be accepted.

The mean pantothenic acid activity of the high cost diets averaged 16.3 mg. per day with a range of 13.3 to 19.2 mg., while the mean content of the low cost diets was 14.2 mg. with a range of 9.9 to 20.5 mg. The "poor" diets averaged 6 mg. daily with a range of 5.2 to 7.2 mg. Thus the "total" pantothenic acid activity of the diet of the usual adult living in the United States may be expected to vary from 10 to 20 mg. daily.

Although the metabolic occurrence of pantothenic acid as part of the coenzyme-A molecule is certain in man, a clear dietary requirement has not been established. Short-term balance studies[19] revealed that the total urinary and

fecal excretion of this nutrient equalled or exceeded the daily intake. However, these balance studies were of such short duration that the adequacy of the intake studied (2 to 7 mg.) cannot be appraised. Data on fecal excretion suggest that considerable bacterial synthesis may occur, but it has not been demonstrated that the vitamin synthesized in the gastrointestinal tract is available. Studies of Bean and co-workers,[20] in which pantothenic acid deficiency was produced in man by feeding the antagonist omega methyl pantothenic acid, do not permit a quantitative estimate of a requirement of the vitamin.

Williams[14] recommended that 10 mg. of pantothenic acid would be a safe level of intake, even under conditions of pregnancy and lactation. Our data indicate that this suggested intake easily can be attained because of the ubiquitous distribution of pantothenic acid among common foodstuffs of both plant or animal origin. However, there is little basis for judging the adequacy of this level.

The vitamin B_{12} content of the diets varied widely from 1 to 85 μg. daily. The average values for the high cost, low cost and "poor" diets were 31.6, 16, and 2.7 μg. with ranges of 4.1 to 85.5, 1.2 to 75.6 and 1.1 to 8.1 μg., respectively. Few data are available on the dietary intake of this nutrient. The values found for the adequate diets in this study are much greater than the estimates of Jolliffe and Peterman[21] who suggest that a good diet may furnish as little as 6 μg. daily. No explanation for this difference can be offered, but it should be emphasized that the vitamin B_{12}-replacing effect of desoxyribosides for bacterial growth was measured and corrected for in the present study by assaying before and after alkaline hydrolysis which destroyed the vitamin B_{12}. The rather remarkable difference in vitamin B_{12} content between the adequate diets and "poor" diets emphasizes the importance of the contribution made by meats and other animal products to vitamin B_{12} intake. Even though the poor diet was not completely devoid of animal protein, its vitamin B_{12} content was rather low. It is not surprising that Wokes and coworkers[22] reported that some persons existing on solely vegetable diets in Britain exhibited clinical and biochemical signs of vitamin B_{12} deficiency.

Estimates of the human vitamin B_{12} requirement have been made from observations of patients with pernicious anemia. In these vitamin B_{12}-depleted subjects the amount of vitamin B_{12} needed for attainment and maintenance of good hematologic status can be titrated within rather narrow limits. Darby and others,[23] by using this technic, estimated that the requirements for vitamin B_{12} by normal adults can be met by dietary intakes of 0.6 to 2.8 μg. daily, with the narrower range of 0.6 to 1.2 μg. found to be sufficient for most persons. Accordingly, these dietary analyses indicate that a normal adult eating adequate diets of the type described would obtain sufficient vitamin B_{12} to prevent primary deficiency. In fact, the amount present in the typical diets containing ample amounts of meat and other animal products would appear to be far in excess of that actually required and absorbed. Conversely, "poor," predominantly vegetable diets, containing limited amounts of calories, protein and members of the vitamin B complex, provide a low intake of vitamin B_{12}. Nevertheless, since vitamin B_{12} is absorbed well by normal subjects this small amount is sufficient to meet the minimal estimated requirements. The considerable storage of vitamin B_{12} which can occur, the small quantities of vitamin B_{12} required minimally, and the amounts present even in "poor" diets in the United States are important factors in determining the rarity of dietary deficiencies of this vitamin.[24] These considerations are consistent with the observations that such deficiencies as have been reported are found in strict vegetarians.

This study defines practical intake levels that may be encountered in diets which are expected to support good health in the average adult. It does not set minimal levels of requirements. Knowledge of such levels of intake, however, should be useful as a guide to appropriate levels of nontherapeutic supplementation when and if such are desirable.

SUMMARY

Adequate "high cost" and adequate "low cost" diets were designed according to food

plans published by the Bureau of Human Nutrition and a "poor" diet was selected from data compiled in the Vanderbilt Cooperative Study of Maternal and Infant Nutrition. A one-week menu plan of each type of diet was prepared according to accepted cooking procedures. Representative homogenates of the entire day's intake were analyzed for folic acid, vitamin B_6, pantothenic acid, and vitamin B_{12} using microbiologic procedures.

The results indicate daily intakes of "total" folic acid activity (Str. faecalis 29-21) ranging from 27 to 346 μg. The mean intakes were as follows: high cost, 193 μg.; low cost, 157 μg.; and "poor," 47 μg. The means and ranges of vitamin B_6 intake were as follows: high cost, 2 mg. (1.1 to 3.2 mg.); low cost, 2.7 mg. (1.6 to 3.6 mg.); and "poor," 1 mg. (0.7 to 1.4 mg.). The mean and ranges of "total" pantothenic acid activity were high cost, 16.3 mg. (13.3 to 19.2 mg.); low cost, 14.2 mg. (9.9 to 20.5 mg.); and "poor," 6 mg. (5.2 to 7.2 mg.). The means and ranges of vitamin B_{12} activity were: high cost, 31.6 μg. (4.1 to 85.5 μg.); low cost, 16 μg. (1.2 to 75.6 μg.); and poor, 2.7 μg. (1.1 to 8.1 μg.).

These dietary levels are equal to or greater than the estimates of adult requirements as based on the relatively meager evidence available for vitamin B_6, pantothenic acid, folic acid, and vitamin B_{12}. They provide no support for a concept of widespread dietary lack of these factors. They afford an indication of the expected daily intake and, thereby, should offer some guide to a reasonable level of non-therapeutic supplementation for those who believe that such supplementation is desirable.

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REFERENCES

1. Committee on Dietary Allowances, Food and Nutrition Board: Recommended Dietary Allowances, No. 589, Washington, D. C., Revised, 1958. National Academy of Sciences, National Research Council.
2. Council on Foods and Nutrition: Vitamin preparations as dietary supplements and as therapeutic agents. *J.A.M.A.*, 169: 41 (1959).
3. Bureau of Human Nutrition and Home Economics: Helping Families Plan Food Budget, Mis. Pub. No. 662. Washington, D. C., 1948. U. S. Dept of Agriculture.
4. Darby, W. J. et al. Vanderbilt cooperative study of maternal and infant nutrition. IV. Dietary, laboratory and physical findings in 2,129 delivered pregnancies. *J. Nutrition*, 51: 565, 1953
5. Association of Official Agricultural Chemists: Official Methods of Analysis, 7th ed. 1950.
6. Brodovsky, E. R., Utley, M. H. and Pearson, W. N. Methionine inadequacy of casein hydrolyzate as source of difficulty in vitamin assays. *Science*, 128: 307, 1958.
7. Toepfer, E. W., Zook, E. G., Arr, M. L. and Richardson, L. R. Folic Acid Content of Foods. Microbiological Assay by Standardized Methods and Compilation of Data from the Literature, Agriculture Handbook No. 29, Washington, D. C., 1951. U. S. Dept. of Agriculture.
8. Atkin, L., Schultz, A. S., Williams, W. L. and Frey, C. N. Yeast microbiological methods for determination of vitamins. Pyridoxine. *Ind. Eng. Chem., Anal. Ed.*, 15: 141, 1943.
9. Hoag, E. H., Sarett, H. P. and Cheldelin, V. H. Use of Lactobacillus arabinosus 17-5 for microassay of pantothenic acid. *Ind. Eng. Chem., Anal. Ed.*, 17: 60, 1945.
10. Zook, E. G., MacArthur, M. J. and Toepfer, E. W. Pantothenic Acid in Foods, Agriculture Handbook No. 97, pp. 1–23. Washington, D. C., 1956. U. S. Dept. of Agriculture.
11. Teply, L. J. Personal communication.
12. (a) Bethell, F. H., Sturgis, C. C., Rundles, R. W. and Meyers, M. C. Observations on utilization of folic acid (vitamin B_7) and vitamin B_7 conjugate by persons with pernicious anemia and macrocytic anemia following gastrectomy. *Univ. Hosp. Bull.*, 12: 42, 1946.
    (b) Darby, W. J., Kaser, M. M. and Jones, E. Influence of pteroylglutamic acid (member of vitamin M group) on absorption of vitamin A and carotene by patients with sprue. *J. Nutrition*, 33: 243, 1947.
13. Woodruff, C. W., Peterson, J. C. and Darby, W. J. Citrovorum factor and folic acid in treatment of megaloblastic anemia in infancy. *Proc. Soc. Exper. Biol. & Med.*, 77: 16, 1951.
14. Williams, R. J. Approximate vitamin requirements of human beings. *J.A.M.A.*, 119: 1, 1942.
15. Vilter, R. W. The metabolism of vitamin B_6 in human beings. *Am. J. Clin. Nutrition*, 4: 378, 1956.
16. Snyderman, S. E., Holt, L. E., Jr., Carretero, R. and Jacobs, K. A. Pyridoxine deficiency in human infant. *J. Clin. Nutrition*, 1: 200, 1953.
17. Bessey, O. A., Adam, D. J. D. and Hansen, A. E. Intake of vitamin B_6 and infantile convulsions:

first approximation of requirements of pyridoxine in infants. *Pediatrics*, 20: 33, 1957.

18. Hunt, A. D., Jr. Abnormally high pyridoxine requirement; summary of evidence suggesting relation between this finding and clinical pyridoxine "deficiency." *Am. J. Clin. Nutrition*, 5: 561, 1957.
19. (a) Gardner, J., Neal, A. L., Peterson, W. H. and Parsons, H. T. Biotin, pantothenic acid and riboflavin balances of young women on milk diet. *J. Am. Dietet. A.*, 19: 683, 1943.
    (b) Denko, C. W. et al. Excretion of B-complex vitamins in urine and feces of seven normal adults. *Arch. Biochem.*, 10: 33, 1946.
    (c) Oldham, H. C., Davis, M. V. and Roberts, L. J. Thiamine excretions and blood levels of young women on diets containing varying levels of B-vitamins, with some observations on niacin and pantothenic acid. *J. Nutrition*, 32: 163, 1946.
20. Bean, W. B., Hodges, R. E. and Daum, K. Pantothenic acid deficiency induced in human subjects. I. *J. Clin. Invest.*, 34: 1073, 1955.
21. Jolliffe, N. and Peterman, R. A. Effect of vitamin B_{12} on growth of children. Presented at 50th Annual Meeting, American Association of Cereal Chemists, 1956.
22. Wokes, F., Badenoch, J. and Sinclair, H. M. Human dietary deficiency of vitamin B_{12}. *Am. J. Clin. Nutrition*, 3: 375, 1955.
23. Darby, W. J. et al. Vitamin B_{12} requirement of adult man. *Am. J. Med.*, 25: 726, 1958.
24. (a) Glass, G. B. J., Boyd, L. J. and Stephanson. L. Inverse relationship between intake and utilization of vitamin B_{12} in the intestine. *Fed. Proc.*, 13: 54, 1954.
    (b) Darby, W. J. et al. The development of vitamin B_{12} deficiency by untreated patients with pernicious anemia. *Am. J. Clin. Nutrition*, 6: 513, 1958.

Management of Juvenile Diabetes at Camp Nyda

A Summary of Methods and Results Based on the Experiences in 1957 and 1958

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IN 1961 Camp Nyda will accept diabetic children for a summer vacation for the twenty fifth consecutive year. A considerable amount of data about juvenile diabetes has been collected annually at Camp Nyda. The experience of one camping year is used in formulating policies for the next. Thus, the present system of managing a large number of diabetic children at one time is an evolutionary one derived from the experiences of previous Camp Committees and their chairmen: notably, Drs. H. O. Mosenthal, F. Williams, E. Shlevin, H. Dolger, T. McGavack, A. Jacobi and A. Kantrow. Several studies[1–4] have already been published concerning medical problems encountered at Camp Nyda. The present report was planned to make a comprehensive presentation of the data collected during the 1957 season with reference to the experiences in 1958. These two camping years were chosen because in these years two groups of 100 children each were at the camp for four weeks. Previously three sessions of three weeks had been held. The extra week at camp for a child has not only led to an enriched and more active camping program but has also made the medical observations more valuable.

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There are two guiding policies at the camp. First, emphasis is placed on the fact that each child must begin to learn how to be self-sufficient and how to live normally. To accomplish this, each child is given camping experience similar to that given in camps for normal children. Competitive athletic games, swimming, boating, overnight hikes and "cookouts" are part of the program as well as arts and crafts, dramatics, and journalism. Routine blood sugar determinations and twenty-four–hour collections of urine are not part of the schedule because they interfere with the more important aim, namely, not to be a "hospital in the country." The athletic program contributes to daily and, in fact, hourly variations in the energy expenditures of a child, tending to increase the instability of juvenile diabetes and making frequent insulin reaction one of the major problems in medical management. Enforced rest periods might well prevent these shocks; it is, however, considered more important to educate the child how to prevent and manage such situations as part of the plan to make him self-reliant.

Second, the treatment advised by the referring physician on the application blank is to be followed at camp with minor adjustments in diet and insulin to allow participation in the camping program. This is invariably so unless the home diet is listed as "free." It should be pointed out that the campers have been managed during the other eleven months of the year by many different physicians and clinics. The camp physician follows the prescription

TABLE I

Ranges of Weight of Diabetic Campers
Comparison with Distribution of Weights of Normal Children in a Range of 25 Per Cent Above and Below the 50 Percentile (P25 to P75)

Age (yr.)	No. of Campers		Range of Weight of Normal (P25-P75) Children (lb.)*	Range of Weight of Majority at Camp Nyda (lb.)		No. of Diabetic Children Outside P25 to P75†				
						Over			Under	
	Boys	Girls		Boys	Girls	P75	P90	P97	P25	P10
5, 6	7	2		46–55	53–55	1 0	1 —	1 —	0 0	— —
7	5	10	48.1* – 58.7**	55–59	51–63	2 4	0 4	2 3	0 1	— 0
8	10	7	53.1* – 65.5**	55–66	59–64	2 2	1 2	1 2	1 1	1 0
9	20	11	57.9* – 72.3**	59–72	57–72	7 2	4 1	2 0	1 0	1 —
10	11	19	62.8* – 79.6**	65–83	62–83	2 4	1 3	1 0	2 2	2 0
11	18	8	69.9* – 89.1**	75–90	74–90	2 3	0 2	0 1	2 0	2 —
12	9	13	77.5**– 98.8*	78–85	80–100	3 5	1 3	0 0	1 1	1 1
13 13	16 —	— 8	83.7 –107.9 89.4 –111.0	82–105 —	— 91–105	3 3	0 1	0 0	4 0	2 —
14 14	13 —	— 3	95.5 –123.0 99.8 –119.7	96–123 —	— 92–97	4 0	2 —	1 —	2 3	0 0
15	11	0	108.2 –135.0	116–128	—	4	0	0	1	0
Total 202			In 50% range: 126 (63%)			53 (26%)	27 (13%)	14 (7%)	22 (11%)	10 (5%)

* Tables quoting the data of Stuart and Stevenson[5] were used. To save space, minimum values for girls* and maximum values for boys** are given. The reverse was done for the age group of twelve years. This gives a range that is about 4 pounds larger but in selecting the "over" and "under" ranges, the true values of the tables were used.

† First line represents the number of boys; the second line; the number of girls.

of the child's physician while attempting to (1) avoid insulin reactions, (2) prevent ketonuria, (3) eliminate the symptoms of polyuria and polydipsia, and (4) maintain adequate nutrition. The basic treatment of the child with diabetes is altered only in occasional cases. On returning home from camp the child is instructed to resume former treatment and to see his physician within five days. The physician at the same time receives a card concerning the diabetic regimen at camp.

CASE MATERIAL

It has been estimated that there are about 1,300 children with diabetes between the ages of five and fifteen in the greater New York area. Each year, the New York Diabetes Association receives about 250 applications for camping but there is space for only 200 campers. The children are selected on "priority standards." Newly discovered children with diabetes and children who have never been at camp previously are given first priority. Children living in the greater New York area receive first preference. Those with social home problems (both mother and

father employed) or urgently requiring the health education features given at camp are also selected first. One hundred and twenty boys and eighty girls are thus chosen by the camp director (an educator) and the administrative secretary.

After the selections are made, physicians of the "Medical Intake Committee" survey the medical records. At camp, the children are so billeted as to have ten of the same age in the same bunk with two counsellors.

The data to be presented concern the insulin, diet and nutritional status for each child both at home and at camp according to his or her bunk. It is hoped that this information will be used by other camp committees in the future to make comparative studies.

JUVENILE DIABETES IN THE NEW YORK AREA

Children who attend Camp Nyda, unlike many other camps for diabetic children, have not been treated according to any single "school" of diabetes. They not only differ widely in types of medical treatment but also in social and economic backgrounds. In some instances, treatment has been directed by a well known "conservative" specialist in diabetes and actually carried out by an intelligent child who is supervised by well informed parents. At the other extreme, there are children referred by practitioners who have had little experience with juvenile diabetes and come from ethnic groups where parents prepare only their traditional high carbohydrate menus. With such a spectrum of backgrounds, the question arises as to whether the picture of juvenile diabetes seen at Camp Nyda presents unusual or distinctive features.

From the nutritional viewpoint the picture is favorable; the children are, for the most part, well nourished. The historic picture of the undernourished as well as underdeveloped diabetic youngster is very rare. In Table I statistics are given concerning the nutritional status of the children on coming to Camp Nyda. This was determined by recording the weights of the children in each age group from the highest to the lowest. The range including the weights of the majority in a group was selected by excluding those which were extremely high or low. For the most part, the extremes were eliminated from the range when they were either high for the next age group or low for the age group below. The results of this arbitrary grouping demonstrated a close correspondence to the ranges of weights (P25 to P75) around the 50 percentile; after minor changes were made, they could be compared to the data calculated from a group of normal children studied by Stuart and Stevenson.[5] The weight of over 60 per cent of Camp Nyda children fell into the range considered normal for 50 per cent of the normal children. The distribution around the 50 percentile, which should be uniform, showed a trend for diabetic children to be overweight; fifty three children at Camp Nyda were over, compared to twenty two children who were under the range. A perusal of the percentages given in the column "over the 75 percentile" in Table I indicates the tendency to obesity in some cases. Apparently this trend is not new. Jacobi[2] found 43.2 per cent of the children at Camp Nyda in 1951 to be overweight according to the tables of median weight and height published by the American Child Health Association. Danowski[6] showing the weights of diabetic children in Pittsburgh in terms of percentiles (chart P397[6]) also showed a greater number distributed above the 50 percentile; this was not true for height in his chart.

In addition to nutritional status, the question of comparative insulin requirements was studied. Because of the varied backgrounds of the children (some treated with restricted diets, others with free diets; some oversheltered by their parents, others allowed unrestricted activity) the insulin dosage that was found optimum for each child at the *end* of his or her stay at camp rather than the home dose was used for the survey. The method of obtaining the ranges of insulin was similar to that employed for the weight study. The insulin dosage required by the majority of children in each age group is shown in Table II; those above or below these ranges are also indicated. For comparison, the average figures quoted for the same age groups by Danowski[6] are included. For the most part, the majority of the children at Camp Nyda fall into ranges that have decreased low limits and those who exceed the maximum are not very numerous.

TABLE II
Range of Insulin Dosages at Camp

Commonly Used Approximation of Insulin Dosages*		Insulin Dosages at Camp Nyda					
Age (yr.)	Range (units)	Age (yr.)	Sex	No. of Campers	Range of Insulin in Majority (units)	No. of Campers†	
						Over Range	Under Range
4–8	20–30	5–8	Boy	12	10–24	1 (57)	0
		6–8	Girl	12	10–28	3 (32, 34, 47)	1 (8)
8–12	30–40	8–10	Boy	29	18–32	3 (38, 38, 40)	1 (14)
			Girl	18	18–32	1 (38)	0
		10–12	Boy	30	18–46	2 (56, 61)	1 (8)
			Girl	26	24–48	0	1 (16)
12–16	40–60	12–14	Boy	26	28–48	5 (56, 56, 66, 72, 98)	3 (15, 16, 20)
			Girl	21	28–52	3 (58, 60, 66)	1 (24)
		14–16	Boy	24	34–52	4 (60, 64, 68, 82)	1 (4)
		14	Girl	3	40–48	1 (70)	0
Total				201		23 over	9 under

* Quoted by Danowski.[6]
† Figures in parentheses represent dosage of insulin.

The lower insulin dosages used at Camp Nyda may be due to the vigorous exercise undertaken there by the children as much as to the fact that children with recent onset of the disease are given priority for admission. It had been hoped that these statistics could be used as a guide for our "Intake Committee" to uncover those children who had been receiving too much insulin at home. Unfortunately the ranges are too wide to be of such use.

JUVENILE DIABETES UNDER CAMPING CONDITIONS

As previously stated, care of the diabetic child at camp is considered a continuation of the care given at home. Thus the insulin prescriptions of the referring physicians are followed and the children are given the same type of insulin or the same mixtures which they had previously taken. Since increased physical exercise is anticipated, moderate reductions in the dosage of insulin are made. In 1957, the initial dosage at camp was 10 per cent less than that given at home for all children taking 20 units or more. The reduction was made equally in both insulins if multiple types were used. In children receiving less than 20 units, reductions were made only in unmodified insulin if used along with the longer acting type.

A Medical Intake Committee makes these modifications for camp as applications are received. Time is a factor worth mentioning here because the applications recording the dose of insulin given at home are received from March to May. In 1957, an accurate count revealed that 200 children had seventy one changes in insulin dosage from the time the application was filled out until their arrival at camp in July or August. Most of the changes were small, in the order of an increase or decrease of approximately 5 units; but some were radically different. This can only be ascertained by mailing a special card to the parents with instructions to have it brought to camp by the child with a record of the most recent dose of insulin.

TABLE III

Final Diets Given Girls at Camp (1957)
Comparison with NRC Recommendations — Weight Changes ± 1 Pound or Greater in One Month

Age Group (yr.)	Recommended Caloric Intake (NRC 1958)	Total Campers (no.)	No. of Campers on Final Diet						Gained Weight (no.)	Weight Same (no.)	Lost Weight (no.)
			I (1,800 cal.)	II (2,100 cal.)	III (2,400 cal.)	IV (2,700 cal.)	V (3,000 cal.)	VI (3,500 cal.)			
6–7	1,700	2	0	2	0	0	0	0	1	0	1
7–9	2,100	17	1	10	6	0	0	0	7	4	6
9–10		11	0	3	7	1	0	0	7	2	2
10–11	2,300	18*	0	7	6	3	2	0	10	5	2
11–12		8	0	0	2	3	2	1	1	1	6†
12–13		13*	0	1	2	7	1	1	7	2	4
13–14	2,500	8	1	1	2	2	2	0	1	2	5†
14–15		3*	0	0	0	1	1	—	3	0	0
Summary of 1957 total		80							37	16	26
Results in 1958 total		79							55	15	9

* One record incomplete.

† Weight loss was desired in three because of overweight. Weight changes, as explained in the text, do not only reflect the food intake. They may be due to improvement in diabetic control or reflect stricter dietary intake at camp.

A system similar to that used for insulin is employed for diets. The Medical Intake Committee notes the diet prescription in each application and calculates the caloric content. To this recommended diet is added 10 per cent more calories for anticipated increased exercise at camp. In order to serve 100 trays at each meal with efficiency and rapidity, and maintain a good degree of accuracy in quantitating the diet, six "standard" diets with increasing caloric contents (Table III) are employed at camp. The Medical Intake Committee then assigns to each child the "standard" camp diet which is nearest in caloric content to the corrected home diet. If "free diet" is indicated as the home one, the Medical Intake Committee assigns a diet judged proper for the child's sex, height and weight. This information along with the corrected insulin dosages is made available to the dietician, camp physicians and nurses before camp commences.

Despite all these precautions, the unstable nature of juvenile diabetes manifests itself from the moment the children arrive at camp. In 1957 the camp physicians reported an incidence of ten to fifteen insulin reactions a day in the younger children during the first week in the first camp session; by adjusting diet and insulin dosages, this was reduced to two to five a day during the last three weeks. With this younger group, about 40 per cent of the reactions occurred in the late morning during physical activities. In the second session, the older children experienced about fifteen to twenty reactions daily during the first week but the majority of reactions occurred during the afternoon.

A similar incidence and pattern of insulin reactions has been encountered annually. In 1958 the initial insulin dosage at camp was kept the same as the home dose; only the diets were increased 10 per cent in caloric value. An average of twenty insulin reactions daily was reported for the first week when the younger children were at camp in 1958 and a slightly higher average for the first week when older children attended. Again, the reactions in the older children were more frequent in the late afternoon whereas in the younger children they occurred in the forenoon.

Symptoms of hypoglycemia were usually mild and were manifested in a variety of ways:

headache, weakness, tremulousness, hunger with sweating, nausea, and dazed feeling. Frequently the symptoms were so bizarre that a "spot check" of the urine had to be made for diagnosis; after the bladder was emptied of urine (which was found glycosuric), a second specimen was obtained a few minutes later and was found to be sugar-free. Not infrequently a "dissembler," wanting special attention was uncovered by this means.

For early recognition and treatment, six nurses are employed for 100 children. A nurse equipped with a bottle of orange juice and sugar is in attendance at all play groups, swimming sessions, and over-night hikes. During the night, a nurse makes "bed rounds" at periodic intervals to detect insulin reactions which might occur during sleep. The bunk counsellors are trained to recognize hypoglycemic symptoms and to report them to the professional staff.

CAMP PHYSICIAN'S FUNCTION IN ADJUSTING THERAPY

All data, urinary sugar and acetone as well as insulin reactions are recorded on a bunk chart. Each evening two camp physicians study these charts and readjust insulin dosages or diets to prevent insulin reactions in some cases and to check excessive glycosuria in others. Changes in one only, insulin or diet, are made at one time for a child. Simultaneous changes in both have been found to lead to poor results with "overshooting" of the aim. Visiting physicians, members of the Camp Committee, make the trip from the city to supervise the camp physicians. At least three such visits are made each week.

A more specific description of the daily clinical picture will clarify the challenging problems of the camp physicians. In the morning, particularly during the first few days at camp, a large number of children will have no glycosuria and no acetonuria on arising. During the day, however, some of these children will be reported as having insulin reactions. Since experience has taught that children frequently take extra large doses of insulin at home to "cover" excessive eating, the physician will order a decrease of 2 to 5 units of the unmodified insulin for the next day. In some children the reduction will lead to glycosuria and eliminate hypoglycemic attacks. In others, the urine specimen will not show any glycosuria the next morning; if the child has an insulin reaction again later in the day, the dosage is reduced further on successive days until no reactions occur.

On the other hand, each day about twenty to thirty children will have 4-plus glycosuria (with or without acetonuria) before breakfast. Rapid screening is performed by the camp physician dividing such children into a symptomatic and an asymptomatic group. The former may be languid, nauseated and anoretic, or have a sore throat, stuffed nose, pink ear drums or diarrhea. These are usually only one to four in number and they are kept on the infirmary porch for observation and treatment. The remaining majority feel perfectly fine and are sent out to play with their group with an order to return in two hours for a recheck of urine. It is not uncommon for two or three of these to have an insulin reaction while at play. Most of these children usually will have a sugar-free urine when subsequently tested in the mid-morning. Acetonuria is also readily cleared by the same management, physical activity. The physician soon learns that exercise is a potent treatment; extra doses of insulin given regularly just because a child has glycosuria or acetonuria on arising can lead to severe reactions. To some extent, the camp physician begins to consider glycosuria on arising a "safety factor" against reactions later in the day. If hypoglycemic episodes should occur in such children, the physician raises the carbohydrate intake during the day to forestall the reactions. Subsequently, the insulin dosage must often be increased to "cover" the extra food.

If glycosuria is not cleared up by exercise but persists until evening, it is an indication that insulin increments must be made until better control is obtained.

Much of what has been said of glycosuria applies also to asymptomatic acetonuria. Dr. Charles B. MacIntosh, the camp physician in 1958, kept accurate records for one month in the younger group of children and

found that in 90 per cent of the children acetonuria was evident in the morning specimen at one time or another. In the evening specimen about 21 per cent of the children had acetonuria intermittently. In no camper did acetonuria appear during the day unless it was present in the morning. By the end of the first week at camp the occurrence of acetonuria in the evening had disappeared completely and that in the morning almost completely. However, in a few cases, the presence of acetonuria as well as glycosuria in the morning persisted for as long as two weeks. Frequently it was necessary to give an additional dose of NPH or lente insulin before supper to control this.

STABILITY OF DIABETES (DIABETIC CONTROL)

Hindsight always finds more logic in a complex situation than foresight; the same can be said for the picture of diabetes presented by the children at Camp Nyda. A survey of the medical charts of each child at the end of the camp session reveals various patterns of response to treatment which can be grouped into four classes for the sake of discussion:

Class A consists of children who are perfectly stable after the first few days at camp. They have no insulin reactions and urine specimens examined before breakfast and dinner are consistently negative for sugar and acetone.

Class B consists of children who, after readjustments of diet and insulin during the first week at camp, no longer have insulin reactions even during exercise. However these children have intermittent glycosuria throughout the camp session.

Class C consists of children who, despite constant attempts to readjust insulin and diet, continue to have frequent, unpredictable and severe insulin reactions. These reactions occur in the presence of seemingly constant mild glycosuria.

Class D includes children in whom ketoacidosis occurs after stress, infection or reduction of insulin.

Many believe that instability is iatrogenically induced by improper selection of the type and quantity of insulin given. They would interpret these classes as merely different degrees of diabetic control due to proper or improper management. However, most physicians who have observed the children at Camp Nyda and their individual responses to the same routine of diabetic treatment are impressed by *inherent* differences in the majority of the children: they vary from those who are easily and well controlled (class A) to those who continue to have episodic hypoglycemia despite almost constant moderate glycosuria (class C). The concentrated physical exercise at camp emphasizes the differences by exaggeration of the response of each child.

Attempts have been made to predict the "problem" cases. In the application for registration at camp, questions are asked concerning the stability or instability of the child's diabetes. The answers, for the most part, have not helped to foretell the child's responses at camp. Moreover, the degree of instability has no relationship to the age group, the status of physical development or the insulin dose. For instance, the incidence of insulin reactions in the first month with younger children is as great as during the second month with older children who receive larger doses of insulin. However, despite the equally labile nature of their diabetes, management of the former group is easier because small decreases in insulin or small increases in the carbohydrate content of the diet are very effective; in the older group, wider changes are necessary. It is for this reason that the younger children who are more easily manageable are taken to camp during the first session; during this easier time the staff comes by its training and is able to cope with the older more challenging group the next month.

STABLE CASES (CLASS A)

Of the 200 children at camp, only twenty eight (14 per cent were found to have urinalyses that were sugar-free twice daily most of the time while having no insulin reaction during the latter part of their stay at camp. These children were distributed throughout all age groups. It is well known that juvenile diabetes may remain "mild" for several years before an inevitable progression to a more severe form occurs. Of these twenty eight

children, all but seven had diabetes less than two and a half years. Since many cases in class B and class C were also of short duration, this factor cannot be used as a guide in predicting the stability of a particular child. Nor could such a child be identified by the insulin requirements; these were usually in the same range as those with unstable diabetes in the same age group.

Although the camper with sugar-free urine and absence of insulin reactions was usually simple to manage after the first week, five such children presented the most serious problems at camp during the first week. They had severe and frequent reactions daily despite progressive decreases in insulin dosage; stability was only manifested when the daily insulin had been reduced from 88 to 48 units, 65 to 28 units, 110 to 36 units, 40 to 4 units and 100 to 70 units, respectively. Obviously these children could not have been adhering to prescribed diets at home and had been taking additional insulin to "cover" the extra intake.

Anxiety to avoid reactions occasionally leads the camp physician into increasing the diet or decreasing the insulin dosage excessively when he encounters constantly sugar-free urine specimens. In the retrospective survey of the charts, it seemed that this happened in two patients who for a while demonstrated stability but later had moderate glycosuria. In only two of this entire group did the insulin have to be increased over the dose given at home and these changes were in the order of 2 units.

MOST COMMON PATTERN (CLASS B)

In the description of a "typical day" in the medical management at camp, the allowance of mild glycosuria to prevent hypoglycemia was discussed. Of the 200 campers, 145 continued to have such glycosuria. None had symptoms of decompensated diabetes, most gained weight, and when acetonuria occurred it was transient.

In forty-two of the 145 children, insulin had to be reduced more than 4 units because of hypoglycemic episodes. Of these, twenty-eight had reactions so frequently and severely that they seemed super-brittle. However, by decreasing the insulin dosage and increasing the carbohydrate intake, insulin reactions no longer occurred after the first week at camp. These children, however, had intermittent glycosuria for the remainder of the session. It was found that the insulin could be increased in thirty-five cases but in sixty-seven the dosage at camp was eventually left to be the same as at home for reasons which appear subsequently.

The question has been raised as to whether better control of the diabetes might be obtained if radical manipulations of the insulin were employed such as giving new combinations of long and short acting types. It is the belief of the majority of attending physicians to Camp Nyda that not many cases would be helped. The children in class B seem inherently to swing from hyperglycemia to hypoglycemia after slight changes in insulin, diet and exercise. Two incidental observations seem to confirm this. First, on rainy days at camp when there is less physical exercise, glycosuria in this group becomes excessive; in clear weather with full activity, the same children often have hypoglycemia without any changes in diet or insulin dosage. Secondly, attempts to decrease the incidence of glycosuria by routinely raising the insulin dosage as little as 2 to 5 units in all campers having glucose in the urine will lead to insulin reactions in as many as twenty to thirty children until the dose is again reduced. The camp physician who comes to know each child learns to make changes on an individual basis.

It would be of great interest for camp committees to be able to compare the type and degree of diabetic control at home with that attained at camp. Although an attempt to obtain this information has been made through the application form, no clear-cut picture can be derived from the answers obtained. Of the 145 children in class B, 102 were treated at home with a single daily dose of insulin (chiefly NPH, Lente and only a few with globin and protamine). It is difficult to believe that many of these were stable with no glycosuria while on only one dose of insulin at home and that activity at camp upset such regulation. Definite evidence that the referring physician attempted to obtain more careful control was seen in the use of multiple

insulins in forty-three class B children. Unmodified insulin was used to supplement NPH or Lente insulin in twenty-eight; intermediary acting insulin was given twice a day in ten; Protamine-regular mixtures in three; Protamine-NPH in one; and regular insulin "coverage" in one. According to the policy of the camp committee, the combinations were left unchanged, the dosage merely raised or reduced, and yet glycosuria persisted.

"BRITTLE DIABETES" (CLASS C)

There is a small group of children who, despite the liberal concept of diabetic control employed for class B campers, continue to have severe and unpredictable insulin reactions long after these have ceased to occur in other children. In 1957 there were twenty-five such chidlren with "brittle" cases (twenty boys and five girls). For the most part, the time of reactions bear no relationship to the peak action of the insulin they received, frequently occurring during rest period or at night.

Class C is obviously an arbitrary grouping that is distinctive only because of an inability to anticipate the severe hypoglycemic episodes which occur once or twice a week. This happened as often in the children in the younger age group as in the older age group. There are no distinguishing features to allow a clinical differentiation from the other campers, except that seventeen of the twenty-five had had diabetes for more than half their lives; only five had had diabetes for less than two years. Several children were suspected by the camp physician to have deep-seated emotional problems. This group requires further study.

KETOSIS (CLASS D)

This class is also an arbitrary grouping, but it is important because the tendency to acidosis is characteristic of juvenile diabetes. In 1957 during the first camping session, four children were kept in the infirmary for forty-eight hours because of early, symptomatic ketoacidosis. The second month was characterized by cold and rainy weather; there were more infections of the upper respiratory tract and yet no ketoacidosis occurred. However, there was a twelve-hour epidmeic of gastroenteritis during which five campers required the administration of supplementary unmodified insulin on an ambulatory basis because of impending ketoacidosis.

In 1958 during the first month, three boys were treated in the infirmary for ketoacidosis and six additional children were treated for ketonuria on an ambulatory basis with a few doses of supplmentary insulin. During the second month, despite many mild infections of the upper respiratory tract, there were no infirmary cases and only two or three children required the administration of supplementary unmodified insulin on an ambulatory basis. One girl with cellulitis of the leg was kept in the infirmary.

This infirmary record is significant and probably rivals the record of camps for normal children in the paucity of time lost due to infections. Future employers could well take note.

CHANGES IN INSULIN DOSAGE AT CAMP

To avoid undue hypoglycemia as well as acetonuria during the first week at camp, different formulas have been attempted in the past. In 1951, when children were at camp only nineteen days, the insulin dosage of each child was initially cut 30 per cent. As reported by Jacobi,[2] the dosages had to be raised to that used at home in 49 per cent of the boys and 43 per cent of the girls. In 22 per cent of the former and 25 per cent of the latter the 30 per cent reduction either proved to be right or the amount of insulin had to be reduced further. Hypoglycemia may have been reduced but glycosuria was too often excessive.

In 1957 (Table IV), the dose of insulin was decreased as previously described. It was found that at camp 42 per cent of the children eventually returned to the dose of insulin used at home with minor adjustments of plus or minus 4 units. Only in 17 per cent were increases made over the home dose; in 41 per cent decreases were necessary.

In 1958, no initial decreases from the home dosages were made by the "Medical Intake Committee." Again decreases below the home

TABLE IV

Number of Children Having Decreases or Increases of Insulin at Camp Relative to Dosage at Home (1957)

Age Group (yr.)	No. Cases	No. of Units Decreased					Same	No. of Units Increased				
		Less than 16 Units*	−16	−12	−8	−4		+4	+8	+12	+16	More than 16 units
5–7	9		—	2	3	—	—	4	—	—	—	
7–9	32	1 (48)	1	4	6	9	3	4	3	1	—	
9–10	31	—	2	4	6	6	5	4	4	—	—	
10–11	30	5 (20, 22, 24, 27, 28)	1	1	6	8	1	4	2	1	1	
11–12	26	2 (23, 24)	1	3	1	4	7	5	1	1	1	
12–13	23	—	—	2	6	4	2	3	2	3	—	1 (23)
13–14	24	3 (23, 47, 52)	1	3	5	3	—	1	4	3	1	
14–15	15	4 (30, 32, 40, 52)	1	1	—	3	—	2	3	—	1	
15–16	10	4 (18, 37, 41, 74)	2	—	—	1	1	1	—	1	—	
Total	200	19	62				85			33		1

* Figures in parentheses give total change in insulin units.

dose was needed in 37 per cent but only in 24 per cent were the dosages unchanged (plus or minus 4 units) from the home dose. Increases had to be made in 40 per cent.

There were different physicians at camp each year and they differ as to whether changes in diets or changes in insulin is their preferred method of management. This makes it difficult to compare results annually. However, it is certain that in 30 to 40 per cent of the children, doses at camp are lower than at home.

In Table IV are given the magnitude of the changes that were needed in 1957. The greatest number of changes were in the range of plus or minus 12 units and involved adjustments that are comparatively easily made within three or four days with small daily increments or decrements of insulin. However, in at least 10 per cent of the children, the decreases were in the order of from as little as 18 to as much as 74 units. Excess insulin of this degree must be due to excess caloric intake at home with large doses of insulin to "cover." Under any circumstances, these children would have insulin reactions at camp until this fact was discovered.

In general, slightly less than half the children can be controlled at camp on the home dose. Reduction of insulin "across the board" does not particularly ease the burden of management for the camp physician, since he must raise as well as lower the insulin requirements of the children. Attention to the diet should be more valuable in aiding stabilization.

CHANGES IN DIETS—NUTRITIONAL ASPECTS OF CAMP LIFE

The number and extent of changes in diet at camp have always been greater than those with insulin. In 1957 the diets were increased above that ordered by the "Medical Intake Committee" for 74 per cent of the children in each session; it was decreased in only 4 per cent. In 1958 with the same intake policy, 72 per cent of the older group were given increases, but only 28 per cent of the younger group had augmented caloric intakes.

Attempted analysis of the reasons for so many dietary changes presents a complex picture. Many dietary prescriptions (supposedly the child's diet at home) submitted by the child's physician in the application form

are unrealistically below what is usually considered adequate for the child's age. Since these are used as a basis for assigning diets for camp, the errors must be rectified by increasing the diet at camp.

Even when the dietary prescription is adequate, there is good reason to believe that the majority of the children have been consuming more than the referring physician believes. This problem was carefully studied by Jacobi[3] at Camp Nyda in 1951; it was found that only one-fifth of the boys and one-third of the girls actually followed the diet prescribed at home. The majority ate one and a half to two times more than the amount advised.

To add another complicating factor to the picture, in 1957, 39.1 per cent of the boys and 43.7 per cent of the girls had been given "free diets" by their physicians. The term "free diet" is not easily defined. In some "free diets" the child and parents have been carefully taught a prescribed regimen; they then select the proper foods and properly estimated portions from the family table. Other children are allowed "free" amounts of all foods except those containing concentrated sugar; cake, pastries, candies, and sweet beverages are the only limitations. Finally there are children who have been allowed to eat not only whatever food they want but also as much as they desire as well as concentrated sugar items. The study by Jacobi,[3] quoted herein, found that only 54 per cent of the children on "free diets" had been taking the amount of food considered correct for their age and height.

Thus the policy of the camp committee to follow the physicians prescriptions concerning the diet seems unrealistic. When the problem of increased calories needed to cover the extra physical activity at camp is added to the original errors in diet prescriptions, the undisciplined appetites of some children and the lack of exact knowledge concerning what half the children have been eating at home, the present system of assigning the initial diets to be used at camp seems impractical.

A study designed to see what diets the children were finally given at camp might well give a clue as to the best diets to give initially. In Tables III and V are given the number of children and the caloric contents of the diets they eventually received. Also included for the sake of comparison are the "average" caloric requirements recommended by the National Research Council. It can be seen that with the exception of the girls aged seven to nine years, the caloric content of the diets finally given at camp were greater than the "average" ones recommended. This should be expected in conditions in which activity is increased.

It is acknowledged that overnutrition is to be avoided in diabetes. It is thus important to ascertain whether the increased calories given at camp were actually necessary for the greater energy requirements of the strenuous camp program or for other reasons such as increased appetites. For this reason the number of children who gained or lost over 1 pound in one month are also included. Most changes in weight were small, in the order of 1 to 3 pounds, unless especially noted.

The majority of girls (Table III) received 100 to 400 calories more than the recommended average and this is reflected by weight gains in almost all age groups and in thirty-seven of the seventy-nine girls. The weight losses in the thirteen to fourteen year old girls was due to their request for reducing diets because of their interest in their appearance. In the eleven to twelve year age group, the weight losses in several girls was deliberate because of frank obesity. In general, girls were more satisfied with less food than the boys.

The majority of boys (Table V) eventually received 300 to 500 calories above the recommended average. In the five to ten year old boys, weight loss was commonly seen, but those in the older age groups mostly maintained their weight or gained. In the boys aged thirteen to sixteen years, a 3,600 calorie diet was commonly used; this is about 500 calories above the recommended amount and led to excessive weight gains.

These findings are not meant to be construed as a scientific analysis of the nutritional requirements of diabetic children. It must be remembered that in diabetic children, changes in weight at camp reflect not only the intake of food but also the spillage of glucose and ketones

TABLE V
Final Diets Given Boys at Camp (1957)
(Same Conditions as in Table III)

Age Group (yr.)	Recommended Caloric Intake (NRC 1958)	Total Campers (no.)	I (1,800 cal.)	II (2,100 cal.)	III (2,400 cal.)	IV (2,700 cal.)	V (3,000 cal.)	VI (3,500 cal.)	Gained Weight (no.)	Weight Same (no.)	Lost Weight (no.)
5–7	1,700	7	4	3	0	0	0	0	0	0	7
7–9	2,100	15	0	2	10	3	0	0	4	3	8
9–10		20	0	0	7	5	6	2	5	3	12*
10–11		11	0	0	0	5	6	0	3	6	2
11–12	2,500	18	0	1	1	5	9	2	7	8	3
12–13		10†	0	1	0	6	0	3	3	3	3
13–14		16	0	0	0	3	5	8	10	2	4
14–15	3,100	13‡	0	1	0	0	2	10	3	4	4
15–16		10	0	0	0	0	0	10	6§	3	1
Summary of 1957 total		120							41	32	44
Results of 1958 total		119							68	17	34

* Majority were overweight, see Table I, 9–10 year old group.
† One record incomplete.
‡ Two records incomplete.
§ 3 campers gained 7 to 9 pounds.

in the urine. Loss in weight may also be due to previous overeating; gain in weight at camp may indicate previously poor diabetic control at home. These factors require further analysis. The present data, however, indicate that diets, which by trial and error, were increased at camp surpass the recommended caloric values with a tendency to "overshoot." It would seem advisable that the recommended "average" caloric intake for each age group be used as the "initial diet" for camp with adjustments made for those underweight or overweight. This should lead to less changes while at camp and possibly decrease the number of insulin reactions during the first week.

DIETETICS AND FOOD SERVING

The problem of appetite versus satiety, which is recognized in weight reduction of obese patients, is also important in patients with juvenile diabetics. Hunger is a frequent complaint at camp. Some children have been known to simulate insulin reactions in order to have their diets increased. Others write home that they are hungry although they are overweight and are still gaining at camp. Many have developed a habit for excessive food intake while at home; these same teenagers tend to go to excess in many other emotional drives involving "forbidden fruit."

On the other hand, some of the "hunger" is truly biological, caused by subclinical hypoglycemia created by exercise. This is suggested from the experience of Jacobi who found that when the insulin dosage at camp was initially reduced 30 per cent, only one-third of all children received increases in diet and the largest diet contained only 2,860 calories for the older boys in contrast to 3,500 calories found necessary to satisfy the present group of older boys. The hypoglycemia and acutely produced hunger due to exercise in diabetic children occur in relation to activity. The timing of feeding is important and increases in the overall carbohydrate content of the meals may not

prevent hypoglycemia at the time of the concentrated activity.

Many changes in the serving of food at camp may well be tried. Provisions for larger and substantial mid-morning and mid-afternoon feedings should be made. This can be done without radical changes in the present system by substracting milk and bread from lunch and serving it mid-morning; the same could be done in the mid-afternoon with food subtracted from the evening meal. This type of diet more closely approximates the regimen at home where many children get milk and crackers at school in the mid-morning and then "raid" the ice box on coming home from school in the mid-afternoon. During the summer many children prefer "ades" at meals; sugar-free drinks of this sort are available.

As far as the problem of "satiety," dietetic experimentation might well be attempted in several directions. Since five children and a counsellor eat at one table, a "family platter" containing the meat and low carbohydrate vegetables for all six might be served. The children could be allowed to take unlimited amounts of the latter. For the older children, the elimination of a glass of milk would allow a larger portion of meat, potato and butter in equivalence; these may be more satisfying. Experimentation of this type might well find a way to satisfy appetites without necessarily increasing the caloric content of the diets.

SUMMARY

A review of the problems in managing 200 children with juvenile diabetes at a summer camp has been given. Some of these problems arise from changes of environment particularly due to increased activity at camp but they also reflect the unstable nature of juvenile diabetes. Some difficulties arise as a result of a different type of management from that at home. However, with adjustments of diet and insulin, diabetic children can within a short time participate in a normal camping program without any greater morbidity than normal children in other summer camps. Education of the child at camp regarding the nature of the changes required to manage his or her diabetes under different environmental conditions results in a more self-reliant person.

REFERENCES

1. Jacobi, H. G. Nutritional standards, organization, and management of summer camps for diabetic children. *J. Clin. Nutrition*, 1:384, 1953.
2. Jacobi, H. G. Nutritional studies of juvenile diabetics attending summer camp. *J. Clin. Nutrition*, 2:22, 1954.
3. Jacobi, H. G. The food consumption of juvenile diabetics; evaluations of diets used at home and at summer camps. *J. Clin. Nutrition*, 2:343, 1954.
4. Rabinowitz, B. and Kuhnlein, E. Treating juvenile diabetics at Camp Nyda. *New York J. Med.*, 58:2515, 1958.
5. Scientific Tables: Documenta Geigy, pp. 260–265. Basle, J. R. Geigy, 1956. From data quoted by Stuart, H. C. and Stevenson, S. S. Mitchel-Nelson Textbook of Pediatrics, Philadelphia, 1950.
6. Danowski, T. C. Diabetes Mellitus: With Emphasis on Children and Young Adults. Baltimore, 1957. Williams & Wilkins Co.
7. Newman, K. J. Nutritional Needs of children after infancy. *New York J. Med.*, 59:3252, 1959.

An Interracial Study on the Serum Protein Pattern of Adult Men in Southern Africa

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The epidemiologic approach can be of great value when one wishes to assess the effects of a life-long exposure of a particular factor, but one is frequently faced by difficulties in the interpretation of the data obtained. With respect to the serum protein pattern of subjects in Africa, one is confronted by the interplay of the effects of tropical disease, the life-long dietary inadequacy of the Bantu,[1] and genetic factors in the comparison with findings elsewhere.

These difficulties were confronted during a survey in 1952 on Bushmen and Bantu residing in the tropical disease environment of the Okavango River Territory of Northern South West Africa. For example serum protein patterns[2] in these two genetically distinct racial groups were similar, but on comparison with Bantu residents in the nontropical disease environment of Cape Town, there were vast differences. As Okavango Bantu and Cape Town Bantu are genetically similar and have similar dietary customs, one could interpret these differences as being due to the effect of tropical disease. Tropical disease, however, could not explain the differences of a similar nature that existed when these Cape Town Bantu were compared with Cape Town white subjects of European descent. In the study of these groups the gamma globulin levels decreased in magnitude from tropical Bantu to nontropical Bantu to European subjects while the reverse was true of the serum albumin level. In 1955, we decided to extend these studies by incorporating the genetically distinct Cape Colored population, who are on an intermediate situation on the socioeconomic scale,[3] in order to attempt to study the factors responsible for these different serum protein patterns.

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MATERIAL AND METHODS

The subjects sampled were actively engaged in industry and subscribed to the fact that they felt well. They had no abnormal physical signs on clinical examination; the hemoglobin levels and packed red cell volumes were within the normal range;[4] and tests performed conventionally to assess liver function revealed no abnormalities.[5] The erythrocyte sedimentation rate was recorded for each subject.[4] Approximately 600 men between the ages of twenty and sixty years, from the three racial groups (European, Cape Colored and Bantu residents in the Cape Peninsula) were sampled. Serum samples from 320 of these were subjected to paper electrophoresis.

From each subject, facts about his income, occupation, family size and nature of his customary diet were obtained. The dietary data were obtained by a system of recall, in that the subject described his usual diet during the week and week-ends. In the quantification each man was rated as having consumed an average portion and the protein, carbohydrate and fat content thereof was in that way obtained.

Horizontal filter paper electrophoresis[6] was carried out on Whatman No. 1 filter paper. The serum was applied by means of thin filter paper strips, and after fractionation the dried papers were stained with Azocarmine B and washed with dilute acetic acid; first, with a 10 per cent ethanol solution, then with an aqueous solution.[7] Elution with dilute alkali (0.1 N NaOH) and spectrophotometric estimation at 500 mμ. revealed a small but appreciable paper blank which was corrected for by proportional subtraction from each fraction before the percentage contribution was calculated.

TABLE I

The Serum Protein Pattern of Apparently Healthy Bantu Subdivided on the Rate of Erythrocyte Sedimentation

Bantu	Total Protein (gm./100 ml.)	Albumin (gm./100 ml.)	Globulin (gm./100 ml.)			
			$Alpha_1$	$Alpha_2$	Beta	Gamma
117 subjects with E.S.R. less than 8 mm./hr.	7.79 ±0.50	5.15 ±0.61	0.24 ±0.11	0.44 ±0.14	0.57 ±0.12	1.39 ±0.21
50 subjects with E.S.R. more than 8 mm./hr.	7.78 ±0.54	4.79 ±0.58	0.25 ±0.09	0.46 ±0.14	0.56 ±0.13	1.71 ±0.38

NOTE: As highly significant differences existed in the serum albumin and gamma globulin levels ($P < 0.001$), all subjects with an erythrocyte sedimentation rate (E.S.R.) exceeding 8 mm./per hour were excluded from further analysis.

The absolute values for each protein fraction were computed from the total serum protein which was determined by the copper sulphate specific gravity method.[8] This in turn was checked by microKjeldahl estimation of protein nitrogen, and the equation used, $P = 377\ (g - 1.0071)$, representing protein concentration in gm. per 100 ml. and g the specific gravity, was found to agree fairly closely with that of Van Slyke et al.[9] The stain produced by the gamma globulin fraction was measured and halved and eluted separately in order to determine whether a faster moving component existed in certain serum samples.

RESULTS

Reproducibility of the Method

Duplicate samples showed excellent agreement in that the standard error of the mean percentage contribution of serum albumin and gamma globulin toward the total protein was 2.7 and 1.3 per cent, respectively. For the beta, $alpha_2$ and $alpha_1$ fractions the figures were 1, 1 and 0.6 per cent, respectively.

Elevation of the Erythrocyte Sedimentation Rate and Its Effect on the Serum Protein Pattern

Approximately 30 per cent of the Bantu, 5 per cent of the Cape Colored and 3 per cent of the European subjects possessed erythrocyte sedimentation rates exceeding 8 mm. per hour. No cause for this was obvious in these apparently healthy working men. Of the fifty Bantu with elevated sedimentation rates only seven were under forty years of age and the majority (70 per cent) originated from the lower income group.

In the Bantu there was a lower mean serum albumin and a higher mean serum gamma globulin level than in Bantu with sedimentation rates below 8 mm. per hour ($P < 0.001$) (Table I). Similar deviations were seen in European and Cape Colored subjects, but in both these two ethnic groups the small proportion with elevated erythrocyte sedimentation rates proscribed statistical analysis. As a result, all subjects with erythrocyte sedimentation rates exceeding 8 mm. per hour were excluded from further analysis.

Interracial Differences in the Serum Protein Pattern

The mean serum albumin levels of European and Cape Colored subjects were alike; both were greater than that of the Bantu, exceeding the 5 per cent significance level. The total protein and total globulin increased in magnitude from European subjects through Cape Colored subjects to Bantu, in large measure due to differences in the gamma globulin levels ($P < 0.001$) (Table II). Subdivision of the gamma globulin into two components did not show that the Bantu possessed a greater concentration of a faster moving component.

The Effect of Age

It was noted in each race that the serum albumin level decreased with age and the gamma globulin level increased with age, the total serum protein level remained almost similar. Regression analysis revealed that the slopes were significantly different from

TABLE II

The Serum Protein Pattern of the Three Racial Groups Expressed as gm. per 100 ml. and as a Percentage

Ethnic Groups and No. of Subjects	Total Serum Protein gm.	Albumin		Globulin							
				$Alpha_1$		$Alpha_2$		Beta		Gamma	
		gm.	%	gm.	%	gm.	%	gm.	%	gm.	%
European (133)	7.38 ±0.48	5.31 ±0.46	72.1 ±4.2	0.21 ±0.08	3.0 ±0.8	0.39 ±0.10	5.2 ±1.2	0.53 ±0.11	7.2 ±1.4	0.93 ±0.15	12.5 ±1.7
Cape Colored (68)	7.52 ±0.44	5.32 ±0.43	70.8 ±4.4	0.23 ±0.06	3.0 ±0.7	0.40 ±0.12	5.3 ±2.2	0.52 ±0.10	6.9 ±1.3	1.06 ±0.16	14.0 ±2.4
Bantu (117)	7.79 ±0.50	5.15 ±0.61	66.2 ±6.6	0.24 ±0.11	3.1 ±1.3	0.44 ±0.14	5.7 ±2.3	0.57 ±0.12	7.3 ±1.5	1.39 ±0.21	17.8 ±2.7

NOTE: The serum albumin values for Cape Colored and European are alike and both are significantly different from the Bantu ($0.05 > P > 0.02$). The gamma globulin differences were highly significant ($P < 0.001$).

zero, and that the regression was linear in its relationship to age. The age range of the Cape Colored subjects extended from thirty to fifty-five years (Fig. 1).

The Effects of Income

Each ethnic group was subdivided into an upper and a lower income subgroup considered as high or low for the particular ethnic group, *viz.*, a monthly money income of less than $50 formed the low income Bantu group, and more than that the high income group. In the Cape Colored subjects, the dividing income level was $125 and in the European subjects it was $225. Within both the Bantu and the Cape Colored groups, significantly higher serum albumin levels and significantly lower gamma globulin levels were found in the upper income subgroups. This difference was not seen on subdivision of the more economically privileged European group. Analysis of variance and by regression revealed that this difference dependent on income existed throughout the age range of the subjects in all groups (Fig. 1).

The Effect of the Dietary Protein Intake

Among the variables that could possibly explain the differences in serum levels that were dependent upon race, age and income level was the dietary protein intake. Analysis by regression revealed a significant and linear relationship among those of the lower economic planes but not among the more economically privileged, whose range of protein intake extended to higher levels. On combining the data in all groups, it became evident that the relationship was curvilinear (Fig. 2).

For the convenience of further analysis, this curvilinear relationship could be expressed by two linear equations, neither of which exhibited significant departures from linearity (Fig. 3). In subjects with low protein intake, the regression of the serum albumin level on the protein intake was positive, while the converse held true for the gamma globulin level. In subjects with high protein intake, the regression slopes were not significantly different from zero. With increasing levels of protein intake then, the serum albumin levels (and conversely the gamma globulin level) rose to a maximum and failed to increase thereafter. The transition point for the animal protein intake was 30 gm.; for the total protein intake 50 gm.; and for the adjusted total protein intake, adjusted on the assumption that the vegetable protein intake had half the biologic value as that from animal sources, 40 gm. daily. Unlike the relationship to the animal protein intake, a considerable proportion of the variance between groups in the total protein intake, whether adjusted or not, was taken up

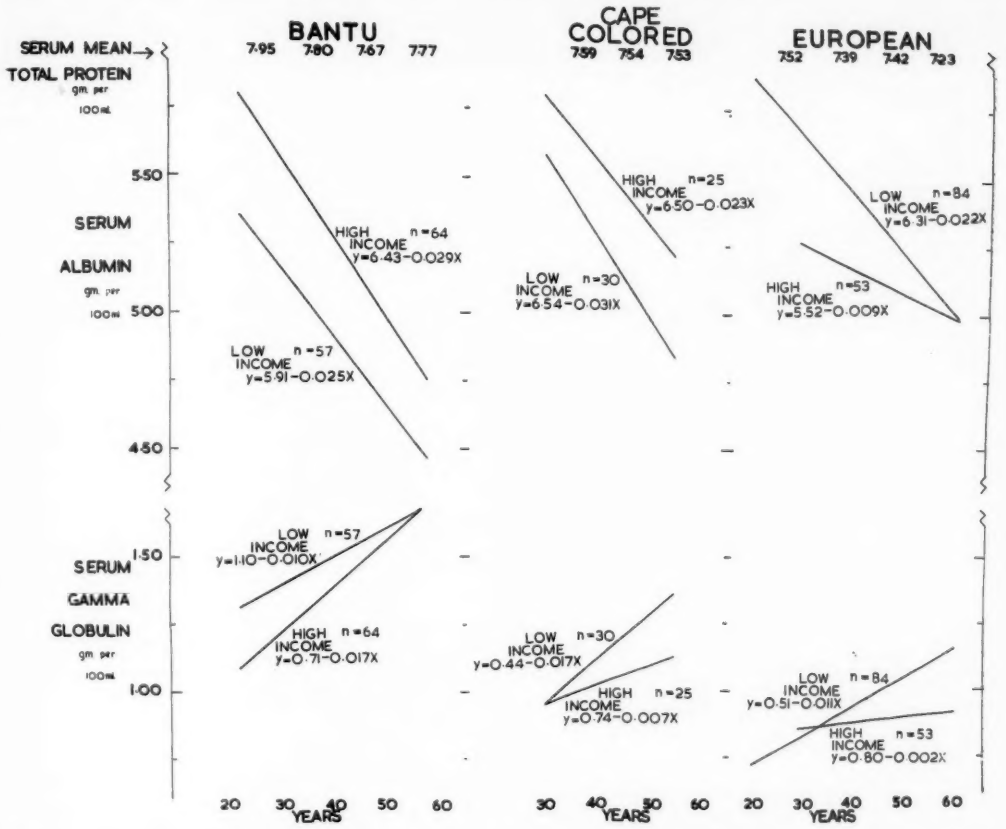

FIG. 1. The serum protein pattern was affected by both age and economic status in these racial groups with the exception of the Europeans in the high economic bracket. The following regression slopes were not significantly different from zero: European high income for both albumin and gamma globulin, Cape Colored gamma globulin for both high and low income groups.

by departures from linear regression, although the variance ratio was not significant ($0.3 > P > 0.2$). No significant relationship existed between the serum level and the vegetable protein intake taken alone.

Interracially, the transition point in the protein intake was the same and no significant differences existed between the slopes of the regression equations for each race (Fig. 3). There were no significant differences in the intercepts of the regression equations for albumin but there were highly significant differences ($P < 0.001$) between races for the intercepts of the gamma globulin equations. It can be noted in Figure 3 that throughout the study the serum gamma globulin levels per unit of protein intake were highest in the Bantu, lowest in the European subjects and intermediately situated in the Cape Colored subjects.

That the albumin and gamma globulin levels were not fully reciprocal in their relation to the dietary protein intake can be shown, too, by the analysis of the difference between the means of these two protein fractions by Student's t test at two levels of the dietary animal protein intake (below and above 30 gm.). Below 30 gm. highly significant differences ($P < 0.001$) exist between both the mean serum albumin and gamma globulin levels of the Bantu and European subjects. Above 30 gm. the serum albumin levels for

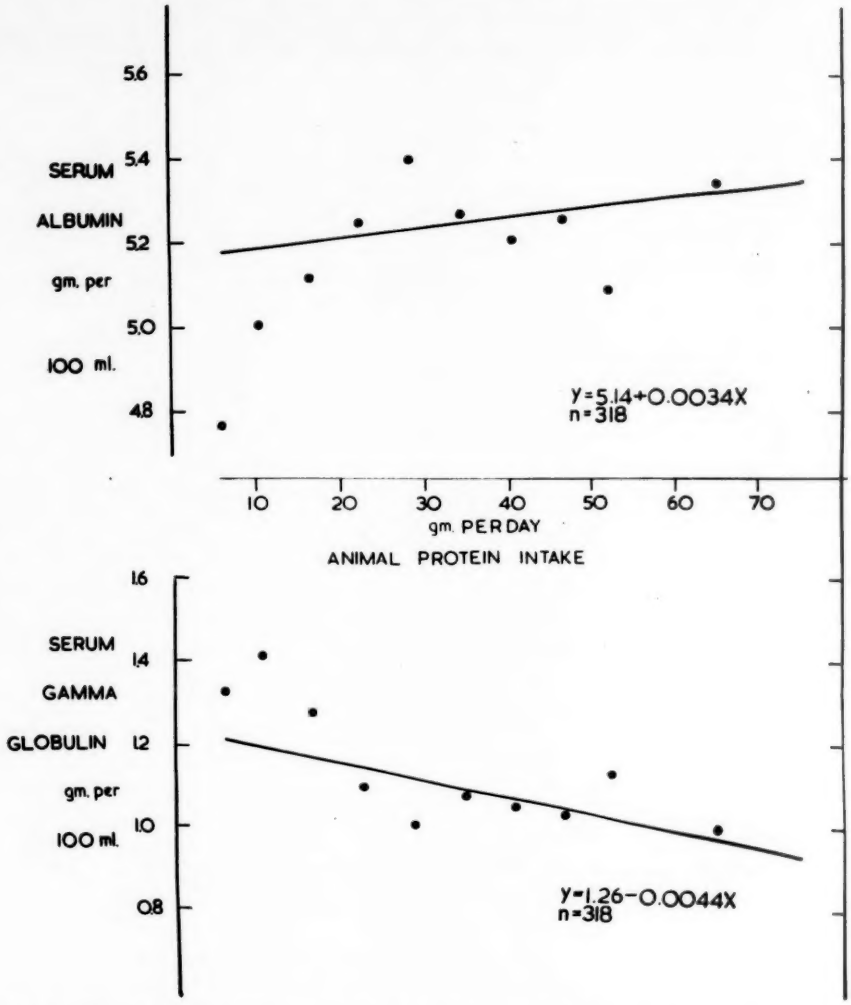

FIG. 2. The relationship of the serum albumin and gamma globulin levels to the animal protein intake for all racial groups. It is shown by regression equations throughout the whole range of protein intake and the means plotted at each level of dietary protein intake. The regression slope for albumin was not significantly different from zero.

these two racial groups are identical (5.25 gm./100 ml.) but the gamma globulin differences remain highly significant ($P < 0.001$) (Table III).

COMMENTS

The Serum Protein Fractionation Technic

The many different methods of serum protein fractionation do not necessarily give comparable results. There are many possible reasons for this[10–12] and the controversy over whether the electrophoretic fractions should be expressed as a percentage or in absolute figures has been emphasized. Unless a correction factor is applied, the albumin levels in paper electrophoretic methods constitute 60 to 70 per cent of the total serum protein,[13] a proportion far higher than that obtained when chemical methods are used. This pro-

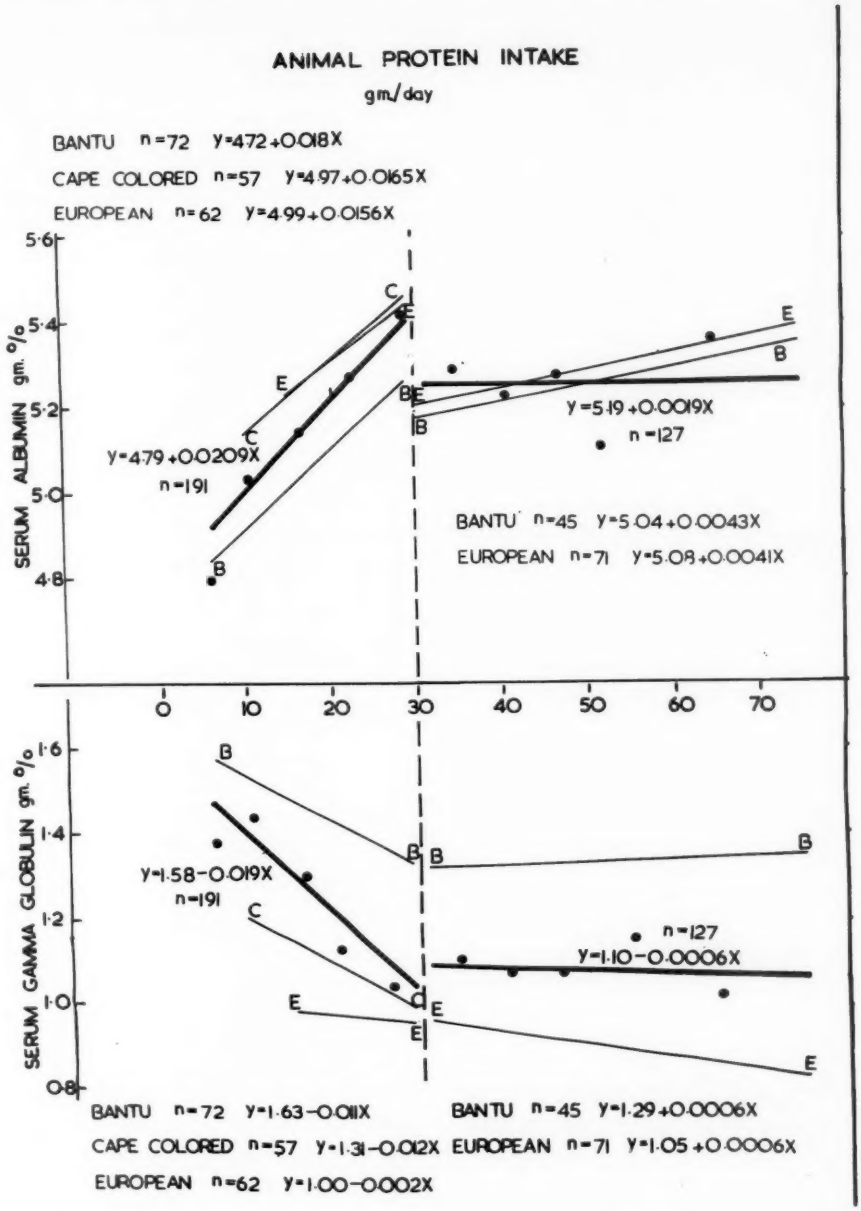

FIG. 3. The relationship of the serum levels to the animal protein intake can best be expressed in two linear regression equations for intakes above and below 30 gm. per day. Above 30 gm. the regression slopes are not significantly different from zero. There were no significant interracial differences in all the regression slopes. Significant differences were seen ($P < 0.001$) on comparing all the gamma globulin intercepts. Serum albumin intercept analysis showed 5 per cent level of significance ($0.05 > P > 0.02$) only in the 0 to 30 gm. animal protein intake range on comparing Bantu with European or Cape Colored. The eleven Cape Colored subjects who consumed more than 30 gm. per day were not included in the figure.

TABLE III
The Serum Albumin and Gamma Globulin at Two Levels of Protein Intake

Ethnic Group and No. of Subjects	Animal Protein Intake (gm./100 ml.)	
	Serum Albumin	Serum Gamma Globulin
Below 30 gm. Daily		
Bantu (72)	5.06 ±0.59	1.43 ±0.33
European (62)	5.36 ±0.53	0.95 ±0.22
Above 30 gm. Daily		
Bantu (45)	5.26 ±0.63	1.29 ±0.30
European (71)	5.26 ±0.39	0.92 ±0.23

NOTE: In the upper ranges of protein intake, the differences in serum albumin levels between these two races are no longer seen, but the gamma globulin differences remain highly significant ($P < 0.001$).

portion is even higher when allowance is made for a paper blank and further differences could be expected if different staining technics are used. Kaplan et al.[11] conclude that each laboratory must have its own method, and comparisons with data obtained by other methods are not justifiable. Unfortunately, in Africa, there are few interracial studies in which the same technics have been used by the same investigators and the groups under study have been examined at the same time.

Interracial Studies in Africa

The consistent difference that has emerged in all studies has been that serum albumin levels are lower and globulin levels higher in the Bantu than in European subjects, the latter being due to higher gamma globulin values. This has been demonstrated in the male,[14–16] in the female,[17–19] and in the child beyond the first year of age.[20] In our 1952 sample,[2] these basic differences were accentuated in the presence of tropical disease and in the presence of elevation of the erythrocyte sedimentation rate in the Bantu.

The reason for the increased sedimentation rate in a considerable proportion of these apparently healthy men is obscure. Walker et al.[21] noticed this among recruits to the gold mines and attributed the change that occurred after a period in the mines as being due to improved diet. In this respect, it is of interest that in our sample, 70 per cent of those exhibiting this phenomenon originated from the Bantu in the low income group. Stanier[22] has drawn attention to the possibility that Bantu possess a faster migrating component in the gamma globulin fraction. Our attempts to study this on filter paper could not confirm this observation.

Interplay of Diet and Exposure to Infection

It is highly probable that more than one factor is responsible for these interracial differences in the serum protein pattern. In non-tropical areas, the prominent environmental factors conditioned by custom and socioeconomic status that differentiate European subjects from Bantu are dietary habits and exposure to infection. Intermediately situated in these respects are the Cape Colored people. The progressive process of urbanization of some of the Bantu and the increasing prosperity of this ethnic group and the Cape Colored people has led to considerable overlap from group to group.[3]

From the genetic point of view one must emphasize the similarity of serum albumin and globulin levels in the newborn white and black races in Africa.[18,19] Differences can be seen following the first year of life.[20] At this stage, in the growing infant, there appears to be little doubt of the relationship of the dietary protein intake to the serum albumin level in that in kwashiorkor the serum albumin level rises rapidly on protein repletion.[23] In the adult there are very few reports that indicate a similar relationship. Stanier and Holmes[24] noted a rise in the serum albumin level when malnourished adults were fed a high protein diet but they report that the high gamma globulin level did not invariably fall. A change in the serum albumin level from 3.1 to 4.2 gm. per 100 ml. occurred after a period of residence in a hostel on a liberal protein intake in fifteen Uganda Bantu students. The

total globulin levels remained unchanged at 3.3 gm. per 100 ml.[15] Schofield,[25] in his study of three groups of West Africans resident in Britain for varying periods of time, concluded that with time the protein pattern approaches close to, but does not completely reach, that of the normal European subject; the failure to do so being attributable to the persistently high gamma globulin fraction.

Although, in many of these studies the conclusions cannot be accepted without reservation, the findings corroborate those in our survey and show that factors responsible for the lower serum albumin levels are not necessarily those responsible for the higher gamma globulin levels. In our survey there is a highly significant association between the dietary protein intake, particularly that from animal sources, and the serum albumin level. The association is curvilinear and would suggest that a luxus consumption level exists over and above which no further elevation of the serum albumin occurs. It is of interest that this change occurs at the same level of intake in each racial group.

An inverse relationship appears to exist between the gamma globulin and albumin levels but this is not consistent. The gamma globulin level decreases as the dietary protein intake increases, but different interracial trends are seen. Unlike the serum albumin levels, comparison between the Bantu and European subjects reveals that the globulin levels are significantly higher in the Bantu at all ranges of protein intake, and at all ages. The levels in the Cape Colored people are intermediately situated. It seems obvious that factors other than the dietary protein intake influence the gamma globulin levels when one notes that, at the higher level of animal protein intake, the mean serum albumin levels of Bantu and European subjects are alike, but highly significant differences exist with respect to the mean gamma globulin levels (Table III). These factors could be genetic or environmental, such as long-continued or repeated exposure to chronic infection. The rise in gamma globulin levels with age even in European subjects in the low income group might support the latter contention, but we have no further data available to offer to allow more than speculation.

We believe it is necessary to point out that with this method of dietary survey an accurate estimate of the vegetable protein intake is more difficult to obtain than the animal protein intake. Consequently, the figures given must be regarded as little more than semiquantitative. Nevertheless, it is of interest that the dietary protein intake levels, after which the serum albumin regression coefficients are not significantly different from zero, approximate the F.A.O. recommended adult minimum requirement for reference protein.[26]

If the level of the serum albumin is an index, this epidemiologic study provides evidence for a luxus consumption level of protein intake in that in these apparently healthy men with serum albumin levels within the so-called normal range, the serum albumin increases as the protein intake increases, but only up to a certain level of dietary protein intake. Above that level no further increase in the serum albumin occurs. This conclusion must, of course, be tempered by the knowledge of the inherent inaccuracies of dietary surveys but the study provides a lead for controlled feeding experiments.

SUMMARY

In 1952 using filter paper electrophoresis the serum protein pattern of European subjects was compared with that of Bantu. The outstanding differences were a lower serum albumin level and higher gamma globulin level in the Bantu. These differences could be reduced by excluding Bantu from a tropical environment or by excluding Bantu from a similar nontropical environment but with elevation of the erythrocyte sedimentation rate. Serum protein patterns were similar in Bantu and Bushmen living in the same tropical environment.

In 1955 the interracial survey was repeated but a sample of Cape Colored subjects was included. Similar interracial differences were found and the Cape Colored subjects, intermediate in the socioeconomic scale, possessed a protein pattern intermediate between that of Bantu and European subjects, particularly with respect to the globulin values.

Within each ethnic group the serum albumin level decreased in magnitude and the serum gamma globulin level increased in magnitude with advancing age.

Subdivisions of each ethnic group into two income categories revealed that the serum gamma globulin level was higher in the low income group while, with the exception of the European, the serum albumin level was lower in the low income group.

Regression analysis revealed a highly significant association between serum albumin level and dietary protein intake in that serum albumin levels increased as protein intake increased, but only up to a certain level. Above that level of protein intake no further rise in the serum albumin concentration occurred.

An inverse relationship existed between the serum albumin and gamma globulin levels, but evidence was presented that factors other than dietary protein intake influenced the level of gamma globulin in the serum.

ACKNOWLEDGMENT

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REFERENCES

1. F.A.O.-W.H.O. Expert Committee on Nutrition. Report on Third Session. World Health Organization. Technical Report Series 72, 1953.
2. Bronte-Stewart, B. and Budtz-Olsen, O. The health and nutritional status of the Kung Bushmen of South West Africa. IV. Biochemical aspects. *South African J. Lab. & Clin. Med.*, in press.
3. Bronte-Stewart, B., Keys, A. and Brock, J. F. Serum-cholesterol, diet and coronary heart disease. An inter-racial survey in the Cape Peninsula. *Lancet*, 2: 1103, 1955.
4. Wintrobe, M. M. Clinical Hematology, 2nd ed. Philadelphia, 1946. Lea & Febiger.
5. Mallen, M. S., Ugalde, E. L., Balcazar, M. R., Bolivar, J. I. and Meyran, S. Precipitation of abnormal serums by Lugol's solution. *Am. J. Clin. Path.*, 20: 39, 1950.
6. Swahn, B. A method for localization and determination of serum lipids after electrophoretical separation on filter paper. *Scandinav. J. Clin. & Lab. Invest.*, 4: 98, 1952.
7. Plückthun, H. and Götting, H. Beitrag zur Methode der Elektrophoretischen Untersuchung der Serumeiweisskörper auf Filtrierpapier. *Klin. Wchnschr.*, 29: 415, 1951.
8. Phillips, R. A., Van Slyke, D. D., Hamilton, P. B., Dole, V. P., Emerson, K., Jr. and Archibald, R. M. Measurment of specific gravities of whole blood and plasma by standard copper sulphate solutions. *J. Biol.Chem.*, 183: 305, 150.
9. Van Slyke, D. D., Hiller, A., Phillips, R. A., Hamilton, P. B., Dole, V. P., Archibald, R. M. and Eder, H. A. The estimation of plasma protein concentration from plasma specific gravity. *J. Biol. Chem.*, 183: 331, 1950.
10. Jencks, W. P., Jetton, M. R. and Durrum, E. L. Paper electrophoresis as a quantitative method. Serum proteins. *Biochem. J.*, 60: 205, 1955.
11. Kaplan, C. M., Weisberg, H. F. and Dow, L. Study of paper electrophoresis: comparison with salt precipitation of serum protein fractions. *J. Lab. & Clin. Med.*, 50: 657, 1957.
12. Henry, R. J., Golub, O. J. and Sobel, C. Some of the variables involved in the fractionation of serum proteins by paper electrophoresis. *Clin. Chem.*, 3: 49, 1957.
13. Jencks, W. P., Smith, E. R. B. and Durrum, E. L. The clinical significance of the analysis of serum protein distribution by filter paper electrophoresis. *Am. J. Med.*, 21: 387, 1956.
14. Quinton, M. H. and Barnes, H. D. The serum proteins of healthy Bantu males. *South African J. M. Sc.*, 7: 42, 1942.
15. Holmes, E. G., Stanier, M. W., Semambo, Y. B. and Jones, E. R. An investigation of serum proteins of Africans in Ugada. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 45: 371, 1951.
16. Arens, L. and Brock, J. F. Some aspects of the serum protein pattern of Africans. *South African J. Clin. Sc.*, 5: 20, 1954.
17. Van Oye, E. and Charles, P. Contribution à ètude de la function hepathique chez la noire africaine. *Ann. Soc. belge. méd. trop.*, 31: 387, 1951.
18. Bersohn, I. and Wayburne, S. A comparison of the serum protein, 'liver-function tests' and serological tests for syphilis in new-born African and European infants and their mothers. *South African J. Clin. & Sc.*, 51: 35, 1954.
19. Stanier, M. W. and Thompson, M. D. The serum protein levels of new-born African infants. *Arch. Dis. Child.*, 29: 110, 1954.
20. Holmes, E. G., Stanier, M. W. and Thompson, M. D. The serum protein pattern of Africans in Uganda. Relation to diet and malaria *Tr. Roy. Soc. Trop. Med. & Hyg.*, 49: 376, 1955.
21. Walker, A. R. P., Fletcher, D. C., Reynolds, P. A., Bersohn, I. and Sonnenfeld, E. D. Reduction to normal levels of high erythrocyte

sedimentation rates in apparently healthy South African Bantu men. *Nature, London*, 177: 480, 1956

22. STANIER, M. W. Serum proteins in Africans. *Nature, London*, 171: 880, 1953.
23. BROCK, J. F., HANSEN, J. D. L., HOWE, E. E., PRETORIUS, P. J., DAVEL, J. G. A. and HENDRICKSE, R. G. Kwashiorkor and protein malnutrition. A dietary therapeutic trial. *Lancet*, 2: 355, 1955.
24. STANIER, M. W. and HOLMES, E. G. Malnutrition in African adults. Serum proteins, cholinesterase and protein-bound lipid. *Brit. J. Nutrition*, 8: 155, 1954.
25. SCHOFIELD, F. D. The serum protein pattern of West Africans in Britain. *Tr. Roy. Soc. Trop Med. & Hyg.*, 51: 332, 1957.
26. F.A.O. Protein Requirements. F.A.O. Nutritional Studies, no. 16, p. 17. Rome, 1957. F.A.O.

Serum Vitamin B_{12} Levels and Incidence of Tapeworm Anemia in a Population Heavily Infected with Diphyllobothrium Latum

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NEXT to Addisonian pernicious anemia, fish tapeworm anemia is probably the most thoroughly investigated of all the vitamin B_{12} deficiency states.[1,2] The anemia is characterized by macrocytosis and megaloblastic bone marrow, and is hematologically, neurologically and clinically identical with genuine pernicious anemia, from which condition it only differs in that the patients have intrinsic factor in their gastric juice. Moreover, spontaneous remission sets in when the worm is expelled.[1] That the condition is due to vitamin B_{12} deficiency has been proved beyond doubt by the demonstration that it is associated with low microbiologic serum vitamin B_{12} levels[3] and that parenteral administration of vitamin B_{12} causes a hematologic remission. The mechanism by which the deficiency state is brought about has recently been studied with radiovitamin B_{12} absorption tests.[4,5] In these, low absorption is observed as long as the worm remains *in situ*, whereas absorption is normalized after expulsion of the worm.

The incidence of tapeworm anemia in D. latum carriers has been believed to be relatively low. In 1926, it was estimated at 1:5,000 to 10,000 worm carriers,[6] but on the basis of more recent data, we have reckoned the figure to be tenfold, 1:500 to 1,000.[7] During the course of our radiovitamin B_{12} studies it became evident that in the majority of the *nonanemic* worm-carriers absorption was likewise inhibited, often being as poor as in patients with genuine pernicious anemia.[5] This observation made us suspect that vitamin B_{12} deficiency might be more frequent in tapeworm carriers than had hitherto been presumed. To study this possibility a research team was sent out to a heavily infected district in Eastern Finland to gather data regarding the incidence of anemia and to collect serum samples which later were assayed for their vitamin B_{12} content. Results obtained from this mass study are reported herein.

MATERIALS AND METHODS

For the field study the Lieksa district in Eastern Finland was chosen, because previous studies[8] had indicated that about 50 (42 to 61) per cent of its population was infected with D. latum. Some other reasons also dictated the choice: communications were relatively good, and owing to the efficiency of the local Red Cross branch, the population was favorably disposed toward this study.

Shortly before the field study began, a representative of the Red Cross visited all the schools in the area, delivering a speech to the pupils and distributing question forms. Every member of the pupils' families over nine years of age was to fill in the form and to visit temporary reception offices installed in schools and dispensaries bringing along a sample of feces. In addition, the inmates of the

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local old people's home were examined. A press campaign was also launched to bring in further population groups.

As a result of these efforts, about 80 per cent of those who received question forms presented themselves for examination. The total number of subjects examined was 1,345. The "school approach" explains why the youngest age group dominates the material. The research team consisted of two physicians (W.N. and M.S.), two laboratory technicians and a varying number of temporary personnel.

At the reception offices every subject was personally interviewed and a number of laboratory tests were performed. The stools were examined microscopically for parasite ova and a blood sample for vitamin B_{12} assay was taken into a thoroughly washed centrifuge tube. After clotting, the serum was separated by centrifugation. The serum specimens were frozen in boxes containing dry ice, transported further in the same boxes and finally stored in a deep-freeze at a temperature of $-25°$ to $-27°$c. Later their vitamin B_{12} concentrations were assayed with Euglena gracilis of the *z* strain, using the method of Hutner, Bach and Ross.[9] Some of the assays were performed as late as one year after collection of the samples. In our experience, the mean normal serum vitamin B_{12} level is within the range of 350 to 400 $\mu\mu$g./ml.

In addition to the examinations described, a number of hematologic tests were performed: determination of the erythrocyte count (visual counting), hemoglobin concentration (ordinary alkaline oxyhemoglobin method, readings with photoelectric colorimeter), volume of packed red cells (a disposable tube method[10]), and erythrocyte diameter (halometrically from smears). If clearly abnormal blood was found, the patient was persuaded to enter a hospital, or other arrangements were made to obtain a complete hematologic examination. This included bone marrow biopsy and radiovitamin B_{12} absorption tests.

Every subject was assigned a number, and the persons performing the various laboratory examinations never saw the name of the patient and did not know of the results of the other examinations. The material was not brought together until all the studies were completed, when all the data were transferred to punch cards. Exceptions to this rule were the clearly anemic patients who were examined more carefully during the field study.

In addition to the data referred to, the patients filled in the question forms which dealt with food habits and possible symptoms of worm infection.

TABLE I
Incidence of a Positive Finding of Tapeworm Ova in the Feces

Age Group (yr.)	Number of Subjects Examined			Per cent with Tapeworm Ova		
	Males	Females	Both Sexes	Males	Females	Both Sexes
9–15	216	308	524	14.8	19.8	17.7
16–30	63	111	174	27.0	26.1	26.4
31–40	44	122	166	29.5	29.5	29.5
41–50	83	136	219	44.6	29.4	35.2
51–60	61	77	138	41.0	31.2	35.5
61–70	24	25	49	41.7	32.0	37.5
71–89	27	48	75	55.6	39.6	45.5
All cases	518	827	1,345	28.8	26.2	27.2

This part of the material has not yet been examined in detail and will be published later.

Most of the data reported herein, as well as their statistical assessment, were obtained directly from the punch cards by means of computers (IBM Calculator 602-A and Accounting Machine 421).

RESULTS

Incidence of Tapeworm Ova

The incidence of tapeworm ova in the feces is reported in Table I. It is seen that the incidence increases with age, being highest in the oldest age group. The over-all frequency is 27.2 per cent, and no clear-cut difference is seen between the sexes.

Since the finding of tapeworm ova in the feces is a sure sign of the presence of the worm, failure to find ova in one sample of feces does not rule out the possibility of actual or recent worm infection, these figures represent minimum values. Furthermore, although comparisons are made between the subjects in whose feces tapeworm eggs were found and those in whom ova were not detected, this must not be interpreted as implying that the latter represent *healthy* control subjects.

Incidence of Anemia

A hemoglobin concentration lower than 11 gm./100 ml. was taken as the criterion of anemia. Such values were found in twenty-

TABLE II

Hematologic Data Relating to the Patients with Verified or Suspect Vitamin B_{12} Deficiency Anemia

Age (yr.)	Hemoglobin (gm./100 ml.)	Red Blood Cells (millions)	Hematocrit (per cent)	Mean Corpuscular Hemoglobin	Mean Corpuscular Volume (cu.μ)	Serum Vitamin B_{12} (μμg./ml.)	Bone Marrow*	Schilling Test† (per cent of oral dose)	
								Before Worm Expulsion	After Worm Expulsion
A. Subjects with Tapeworm Ova in the Feces									
25	6.0	1.56	20	38	128	57	+	0	10.5
23	10.5	3.28	37	32	113	30	+	2.1	27.3
45	6.5	1.89	21	34	111	16	+	0	8.4
56	6.6	1.52	19	43	125	28	+	0	15.1
60	9.9	2.44	31	41	127	20	+	0	9.2
51	10.9	2.85	36	38	126	1	+	1.1	–
69	6.6	1.85	21	36	114	20	+	0	11.9
50	8.8	3.36	33	26	98	77	+?	–	–
25	9.5	3.82	36	25	94	71	+	–	–
42	10.2	3.72	37	27	99	53	–	–	–
14	10.5	4.38	–	24	–	53	+?	–	–
38‡	8.5	2.72	26	31	96	273	+	–	–
B. Subjects in Whose Feces Tapeworm Ova Were Not Found									
40	9.9	3.48	37	28	106	40	+?	–	–
42	10.2	3.20	33	32	103	54	+?	–	–
79	10.5	4.23	35	25	83	62	+?	–	–

* Code: + megaloblastic, +? macroblastic without typical megaloblasts, – normal.

† Standard procedure with 1 μg. oral dose, as described by Gräsbeck.[13]

‡ This patient was currently being treated with vitamin B_{12} and a liver preparation given orally and had received a vitamin B_{12} injection one week before this examination.

two worm carriers (6 per cent) and in twenty-eight controls subjects (2.9 per cent). In the worm-carrier group seven anemic subjects (1.9 per cent of the carriers) can be regarded as having indubitable vitamin B_{12} deficiency anemia with typical blood and bone marrow changes, low serum vitamin B_{12} level and Schilling test values lower than 2.5 per cent (Table II). In addition, there was one other patient with megaloblastic anemia who had quite recently been treated with vitamin B_{12}, which probably explains why the serum vitamin B_{12} concentration was normal. When the results of the vitamin B_{12} assays were ready, it was found that another four anemic worm carriers (1.1 per cent) had low serum vitamin B_{12} levels. Since the anemia was hypochromic, vitamin B_{12} deficiency was not suspected during the field study and Schilling tests were not performed. If these suspect cases are added to the verified cases of vitamin B_{12} deficiency anemia, altogether 3 per cent of the worm carriers had a combination of low vitamin B_{12} level and anemia.

Among the control subjects, only three anemic subjects had vitamin B_{12} levels lower than 100 μμg./ml., representing 0.3 per cent of the control group. The anemia in these cases was macrocytic, but the presence of megaloblasts in the bone marrow could not be demonstrated with certainty.

It is worth mentioning that in none of the accidentally discovered eight cases of megaloblastic anemia was the subject aware of being ill. If these eight cases are taken as a minimum value for the incidence of tapeworm anemia, a frequency of about one case in fifty worm carriers is obtained.

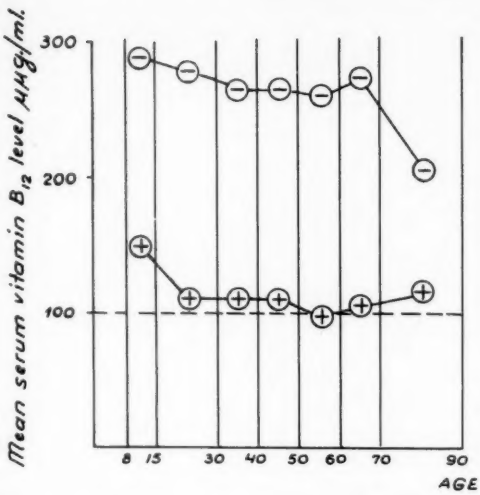

FIG. 1. The mean serum vitamin B_{12} concentrations in the different age groups of the tapeworm carriers (+) and those in whose feces tapeworm ova were not observed (−).

Microbiologic Serum Vitamin B_{12} Concentration

The mean vitamin B_{12} levels in the worm carrier and control groups were 116.4 and 273.8 $\mu\mu$g./ml., respectively. The mean values for the age groups are seen in Figure 1.

Since the presence of anemia may have prejudiced the investigators (these patients received more detailed examination than the rest of the subjects) and the anemia in itself may have had an effect on the serum vitamin B_{12} concentration, the following analysis was made on a reduced series, from which the anemic cases had been omitted.

For the statistical treatment the material was divided into "blocks," consisting of subjects of the same age and sex, and belonging to one of two hemoglobin concentration groups (hemoglobin 11 to 13.9 and $\geqq$14 gm./100 ml.). When the comparisons are made within these blocks, the possibly different distributions of age, sex and hemoglobin concentration in the groups with or without tapeworm ova should have no influence on the result. The serum vitamin B_{12} concentrations in these blocks are given in Table III.

It is seen that without exception the mean vitamin B_{12} concentration was lower in the tapeworm-carrier group. This finding in itself is sufficient to demonstrate the existence of a statistically significant difference.[11] However, the high level of significance becomes more evident when a normal comparison of the means is made within the blocks and the evidence obtained from these twenty-eight comparisons is combined into an over-all significance. This was performed by analysis of variance. For this purpose two estimates for the natural variance were computed, one for the variation between the means in the groups with or without tapeworm ova with 28 degrees of freedom, the other estimate for the variation within the fifty-six blocks with 1,217 degrees of freedom.

The variance ratio $F(28,1217) = 192,548/19,759 = 9.74$ exceeds unity so greatly that the significance level is over 99.95 per cent (for which a variance ratio of 2.10 would have sufficed).

If the differences between the mean microbiologic vitamin B_{12} concentrations of the worm carriers and the control subjects belonging to the same blocks are compared (Table III), it is noted that they are of the same order of magnitude. The median of these differences is 150 $\mu\mu$g./ml. If the assumption is made that the presence of the worm decreases the serum vitamin B_{12} level by 150 $\mu\mu$g./ml., and this figure is added to all the observed concentrations of the worm carriers, the entire material becomes homogenous. An ordinary comparison between the mean concentrations in the fifty-six blocks resulting (variables: sex, age, hemoglobin, presence of tapeworm ova; $2 \times 7 \times 2 \times 2 = 56$ blocks) shows that the differences between the blocks can be explained on the basis of natural variance [$F(55,1217) = 1.20$].

Effect of Age, Sex and Hemoglobin on the Serum Vitamin B_{12} Level

A similar statistical analysis was performed to elucidate the influence of the variables age, sex and hemoglobin ($\geqq$11 gm./100 ml.) on the serum vitamin B_{12} concentration. In dividing into blocks the variable presence or absence of tapeworm ova was taken into account. The variance ratios do not indicate statistically significant effects of age, sex or

TABLE III

Mean Serum Vitamin B_{12} Levels in "Blocks" Consisting of Subjects of the Same Age and Sex and One of Two Hemoglobin Concentration Groups

Block			Control Subjects		Worm Carriers		Difference Between Mean Vitamin B_{12} Levels of Control Subjects and Worm Carriers ($\mu\mu$g./ml.)
Age Group (yr.)	Sex	Hemoglobin*	No.	Mean Serum Vitamin B_{12} Level ($\mu\mu$g./ml.)	No.	Mean Serum Vitamin B_{12} Level ($\mu\mu$g./ml.)	
9–15	F	L	168	284.9	43	141.3	143.6
		N	76	293.7	15	157.4	136.3
	M	L	120	269.3	21	166.9	102.4
		N	60	274.3	11	116.0	158.3
16–30	F	L	50	290.4	18	114.7	175.7
		N	30	261.6	9	72.2	189.4
	M	L	7	187.9	6	94.2	93.7
		N	39	289.2	9	162.1	127.1
31–40	F	L	55	256.7	23	95.9	160.8
		N	23	337.4	8	91.0	246.4
	M	L	1	185.0	6	95.7	89.3
		N	30	236.9	7	100.7	136.2
41–50	F	L	59	271.4	19	108.2	163.2
		N	27	288.4	16	93.8	204.6
	M	L	11	255.2	10	133.6	121.6
		N	35	226.2	27	105.1	121.1
51–60	F	L	26	255.4	12	99.3	156.1
		N	25	271.2	8	100.6	170.6
	M	L	11	215.8	9	88.1	127.7
		N	24	276.8	15	110.4	166.4
61–60	F	L	10	239.2	4	119.8	119.4
		N	7	253.1	3	73.3	179.8
	M	L	3	240.3	1	23.0	217.3
		N	11	319.2	9	122.7	196.5
71–89	F	L	4	274.8	7	107.6	167.2
		N	17	195.6	7	128.0	67.6
	M	L	4	191.0	6	67.3	123.7
		N	5	226.0	6	88.7	137.3
			938†		335†		Median = 150

* Code: N(ormal) = hemoglobin $\geq$ 14; L(ow) = 11 – 13.9 gm./100 ml.

† This is a reduced series; patients with hemoglobin below 11 gm./100 ml. are not included. In addition, a few patients were eliminated because personal or laboratory data were lacking.

hemoglobin in the normal range on the serum vitamin B_{12} concentration.

Incidence of Low Serum Vitamin B_{12} Levels

The effect of D. latum on the serum vitamin B_{12} level is perhaps best illustrated by the incidence of low serum vitamin B_{12} concentrations in the worm carriers. It is generally recognized that serum vitamin B_{12} concentrations below 100 $\mu\mu$g./ml. are pathologic, at least when the assay is performed according to our present technic.[2,12,13] The incidence

TABLE IV

Number of Patients with Serum Vitamin B_{12} Concentrations below 100 $\mu\mu$g./ml. Among Nonanemic (Hemoglobin $\geqq$ 11 gm./100 ml.) Tapeworm Carriers and Control Subjects

Age Group (yr.)	D. latum Carriers		Subjects with No Tapeworm Ova	
	No.	Per cent	No.	Per cent
9–15	93	32.6	431	4.4
16–30	46	53.5	128	3.2
31–40	49	63.6	117	5.5
41–50	77	56.9	142	3.0
51–60	49	56.8	89	6.9
61–70	18	47.1	31	6.7
71–89	34	70.0	41	16.7
Whole material	366	51.6	979	4.9

of values below this level in the nonanemic subjects is reported in Table IV. It is seen that low values were observed in 51.6 per cent (!) of the worm carriers, but only in 4.9 per cent of the control subjects. If the different age groups are compared, low values were significantly (at 99.9 per cent level) less frequent in the youngest age group than in the oldest age group, whereas the other age groups did not differ significantly from each other. Among the control subjects no significant differences between the age groups could be observed.

COMMENTS

The population studied was selected because it was expected that about 50 per cent harbored D. latum. The incidence was found to be only 27.2 per cent, however. Because healthy people would be less likely to respond to our appeal than worm carriers, the true incidence may be even lower. The apparent drop in the incidence (chiefly involving the young age groups) which seems to have occurred since the second world war may be misleading and due to the fact that the earlier estimate[8] was based on indirect observations, whereas the present investigation is the first one in which a true field study has been performed.

However, the best explanation of the change in the incidence is probably the marked improvemenet in hygienic standards which has taken place in the region since the war. This is partly the result of anti-worm propaganda on the part of the local authorities, but perhaps even more due to the general rise in living standard and the industrialization of the region which have changed the dietary habits of the population, especially those of the children and adolescents. For instance, much of the fish eaten is nowadays bought salt-water fish, whereas earlier most had been caught in near-by lakes by the families themselves.

The data demonstrate very clearly that the presence of D. latum markedly decreases the serum vitamin B_{12} level in all age groups. The incidence of tapeworm anemia appears to be at least one case in fifty worm carriers, a figure ten to twenty times higher than has hitherto been suggested.[7] It is quite astonishing that more than half the worm carriers had a pathologically low serum vitamin B_{12} level.

To what extent the serum vitamin B_{12} level reflects the amount of vitamin B_{12} stored in the body is uncertain, although many facts indicate that there is a good correlation between the two, at least when dysproteinemia, liver damage or folic acid deficiency do not complicate the picture.[13] However, it seems certain that a high percentage of the worm carriers suffer from relative, subclinical vitamin B_{12} deficiency. The effects of this subclinical deficiency on health cannot be assessed at the present moment, but harmful effects on fetal development, child growth and general resistance toward infection may be imagined. It is hoped that further analysis of the collected material will shed light on these questions. Since more than 100,000 worm cures are taken per year and several hundred thousand D. latum carriers have been estimated to exist in Finland,[7] which has a population of about 4.4 million, large population groups would appear to suffer from subclinical vitamin B_{12} deficiency. It may therefore be conjectured that D. latum infection will prove to be a much greater public health problem than has hitherto been assumed.

SUMMARY

In order to elucidate the incidence of D.

latum infection, tapeworm anemia and low serum vitamin B_{12} levels, a population in Eastern Finland was subjected to a mass examination. Of the 1,345 subjects examined, 27.2 per cent were found to have tapeworm ova in their feces. Among those who had no tapeworm ova 0.3 per cent had a combination of anemia and low serum vitamin B_{12} level, but none had megaloblastic bone marrow. Among the worm carriers 1.9 per cent had verified (megaloblastic), and another 1.1 per cent suspect (nonmegaloblastic) vitamin B_{12} deficiency anemia. The incidence of tapeworm anemia in worm carriers is at least 1:50. The mean serum vitamin B_{12} levels in the tapeworm carrier and control groups were 116.4 and 273.8 $\mu\mu$g./ml., respectively, the difference being statistically highly significant. More than fifty per cent of the worm carriers had a serum vitamin B_{12} concentration below 100 $\mu\mu$g./ml., whereas this occurred in less than 5 per cent of the control subjects. It is concluded that the incidence of tapeworm anemia is much higher than has hitherto been supposed, that vitamin B_{12} deficiency is extremely common in D. latum carriers and that the D. latum endemy in Finland is thus to be regarded as a serious public health problem.

ACKNOWLEDGMENT

We are greatly indebted to the Finnish Red Cross and its local branch in North Karelia. Our thanks are especially due to Miss Alli Vaittinen for her devoted work in organizing all the practical details before and during the field study. The efforts of Mrs. Alli Rantanen and Lilian Bäckman, and Misses Kerstin Frostell, Astrid Holm, Margaret Johnson and Gurli Wichmann contributed to the success of the investigation. To Martti Tienari, PH.D., we express our gratitude for the performance of the statistical analysis.

REFERENCES

1. VON BONSDORFF, B. Pathogenesis of vitamin B_{12} deficiency, with special reference to tapeworm pernicious anaemia. In: Vitamin B_{12} und Intrinsic Factor, p. 311. Edited by Heinrich, H. C. Stuttgart, 1957. Ferdinand Enke.
2. HERBERT, V. The Megaloblastic Anemias. New York, 1959. Grune & Stratton.
3. NYBERG, W. and ÖSTLING, G. Low vitamin B_{12} concentrations in serum in fish tapeworm anaemia. *Nature, London*, 178: 934, 1956.
4. NYBERG, W. Absorption and excretion of vitamin B_{12} in subjects infected with Diphyllobothrium latum and in noninfected subjects following oral administration of radioactive B_{12}. *Acta Haematol.*, 19: 90, 1958.
5. NYBERG, W., GRÄSBECK, R. and SIPPOLA, V. Urinary excretion of radiovitamin B_{12} in carriers of Diphyllobothrium latum. *New England J. Med.*, 259: 216, 1958.
6. EHRSTRÖM, R. Till kännedomen om Finlands tarmparasiter. (A contribution to our knowledge of the intestinal parasites of Finland.) *Finska läk.-sällsk. handl.*, 68: 684, 1926.
7. VON BONSDORFF, B. Diphyllobothrium latum as a cause of pernicious anemia. *Exper. Parasitol.*, 5: 207, 1956.
8. GYLLING, B. Den geografiska utbredningen av Diphyllobothrium latum i Finland. (Regional incidence of Diphyllobothrium latum in Finland.) *Finska läk.-sällsk. handl.*, 92: 38, 1949.
9. HUTNER, S. H., BACH, M. K. and ROSS, G. I. M. A sugar-containing basal medium for vitamin B_{12}-assay with Euglena. *J. Protozool.*, 3: 101, 1956.
10. WASASTJERNA, C. and NYBERG, W. En mikro-hematokritmetod. (A micro-hematocrit method.) *Nord. Med.*, 55: 58, 1956.
11. SIEGEL, S. Nonparametric Statistics for the Behavioral Sciences, p. 36. New York, 1956. McGraw-Hill.
12. MOLLIN, D. L. and ROSS, G. I. M. The pathophysiology of vitamin B_{12} deficiency in the megaloblastic anaemias. In: Vitamin B_{12} und Intrinsic Factor, p. 413. Edited by Heinrich, H. C. Stuttgart, 1957. Ferdinand Enke.
13. GRÄSBECK, R. Physiology and pathology of vitamin B_{12} absorption, distribution, and excretion. *Advances Clin. Chem.*, 3: 299, 1960.

Iron Content of Intact Placentas and Cords

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THE only significant iron loss during a normal pregnancy occurs at parturition. In addition to the loss of iron to the infant and as result of hemorrhage, iron contained in placental blood, and in placental and cord tissue, is lost. Values for the blood content of a total of 216 placentas were published by several investigators[1–3] and ranged from 9 to 33.4 per cent of the wet weight of the organs. In a study of 143 German women, Mischel[4] found that the total iron in the blood and tissue of the placentas averaged 11.1 and 4.2 mg., respectively, per 100 gm. of wet sample.

More information on the iron content of placentas is needed in the evaluation of the iron requirement during pregnancy. The majority of investigations of this problem have been completed outside the United States, and few details of such factors as diet, prenatal medications and delivery procedures are included, all of which may influence placental iron losses. It appeared worthwhile, therefore, to collect intact placentas and their cords from the delivery room of the State University of Iowa Hospitals in order to evaluate this material in maternal iron loss.

DESCRIPTIONS OF SUBJECTS AND OFFSPRING

The forty-nine patients in this study were not preselected. The pregnancies were considered to be normal, and all resulted in vigorously viable offspring. One patient died of aneurysm four days after delivery although there was no earlier evidence of illness.

Thirty-nine of the patients were indigents who were given custodial care by the hospital for two weeks to one month before term; four patients had insurance which paid hospital fees but not medical fees, and the remaining six were private cases. The subjects were predominantly of northwestern European extraction, but the group included two Negroes and one Mexican. Thirty-five of the women were married.

Pertinent data concerning the pregnant subjects, and their offspring are given in Table I. The mean age of the women was twenty-five years, and the average number of previous pregnancies was two. One obese, nineteen year old patient lost 24 pounds during pregnancy and a sixteen year old adolescent gained 57 pounds, but the group gained an average of 24 pounds. The mean maternal hemoglobin immediately prior to parturition was 11.2 gm. per 100 ml. of blood. Five women had had oral iron medication prescribed by their physicians; however, the regularity of intake throughout the gestation period remains unknown. Six women received intramuscular iron therapy prior to or after admission to the hospital, since their hemoglobin values were below 10 gm. per 100 ml. of blood. The average weight of the infants at birth was 3.1 kg.

COLLECTION OF MATERIAL AND CHEMICAL METHODS

Fifty intact placentas and their cords were collected from the patients upon delivery and were frozen in waxed containers. The standard delivery procedure followed by physicians was to sever the umbilical cord following cessation of the pulsation, allowing the infant to receive as much blood as possible. Two samples from a set of double-ovum twins and two samples from two sets of single-ovum twins were included in this study (Table II).

Aliquots of each suspension of placenta plus cord, which had been partially digested in acid, were ashed and brought to known volumes. A modification of the Woiwod[5] method for

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TABLE I
Pertinent Data Concerning Pregnant Subjects and Their Offspring

Data	Mean	Range
Age (yr.)	25	15–42
Previous pregnancies (no.)	2	0–9
Prenatal weight change (lb.)	24	−24–57
Maternal hemoglobin (gm. per 100 ml. of blood)	11.2	8.2–14.0
Weight of fetus (kg.)	3.1	1.5–4.2

TABLE II
Relationships among Numbers of Subjects, Infants and Placentas

Data	Subjects (no.)	Infants (no.)	Placentas (no.)
Single births	46	46	46
Single-ovum twins	2	4	2
Double-ovum twins	1	2	2
Totals	49	52	50

TABLE III
Iron Content* of Placentas and Cords

Data	Present Study	Mischel[4]
Wet weight of sample (kg.)	560 (385–880)	...
Total iron (mg.)		
Placentas plus cord†	75.5 (34.5–170.0)	
Placenta		63.7
Iron concentration (mg. per 100 gm. of wet weight of sample)		
Placentas plus cord†	13.6 (7.1–34.8)	
Placenta		11.1

* Ranges are given in parentheses.
† Values exclude one sample; see text for explanation.

total iron was employed in which iron in the ashed samples was reduced to the ferrous state and the concentration of the mineral determined colorimetrically with alpha, alpha dipyridyl. Blanks were prepared with the exclusion of the ashed material. Special care was taken in cleaning all equipment to prevent contamination with iron; the pyrex ashing crucibles were treated with 48 per cent hydrofluoric acid.

RESULTS

Data obtained on the fifty placentas and cords were expressed as milligrams of total iron and milligrams per 100 grams of the wet weight of the sample. The results are summarized in Table III.

The total iron content of the samples averaged 75.5 mg. and ranged from 34.5 to 170 mg., excluding one value, 396.7 mg., which was 6 standard deviations from the mean. The latter total iron value was also omitted in the calculation of the iron concentrations in placentas plus cords which ranged from 7.1 to 34.8 mg. with a mean of 13.6 mg. per 100 gm. of the wet weight of the sample.

The weights of the placentas and cords averaged 560 gm. but varied from 385 to 880 gm.

COMMENTS

The data from the current study and that published by Mischel,[4] presented in Table III, agree quite well on the total iron contents of placentas even though the values by the former investigators include iron in the cord. The average placental iron loss of 75.5 mg. was 8.4 per cent of the 900 mg. dietary increment, which has been suggested for pregnancy,[6] while the range extended from 3.5 to 18 per cent, exclusive of the percentage calculation from the single, extreme iron value of 397.7 mg.

Several factors seemed to affect the iron content of the placentas. The wet weights of the placentas appeared to be related to the amounts of blood present in the organs at the time of collection. Salhanick and associates[1] found that the blood contents of nine placentas ranged from 10.6 to 33.4 per cent of the wet weights of the organs. Even though the delivery room procedure was standard in the current investigation, the blood contents of the placentas may be expected to vary considerably. These volumes were not determined, nor was the blood adhering to the sides of the organs after collection separated from samples analyzed for iron.

It is possible that the intramuscular administration of iron-dextran complex preparation to six patients prior to delivery introduced variation in the amount of iron and its concentration in the placentas. The total iron value for one patient who received this iron preparation was 6 standard deviations from the mean. On the other hand, the corresponding value for iron in the placenta plus cord for another patient who received the same dose of iron-dextran complex preparation within a similar time interval before delivery was 1 standard deviation below the mean for the group.

Four of the six patients receiving intramuscularly administered iron were unmarried, which may suggest that social or economic factors influenced the nutritional status of the woman and her offspring. Relationships between the various chemical values or case history information and the oral administration of iron were not apparent. The woman who died of an aneurysm following delivery received no iron supplementation, but the concentration of iron in the placenta plus cord was 34.8 mg. per 100 gm. of the wet weight of the sample, the second highest value found (Table III).

Four placentas were associated with multiple births. The two from one set of double-ovum twins effected a maternal iron loss of 145 mg. The placenta and cord from one of the two sets of single-ovum twins contained 85.5 mg. of iron, while the other represented a loss of only 49 mg.

The twenty-two year old and fifteen year old Negro subjects lost 84.4 and 62 mg. of iron, respectively, due to expulsion of the placenta. Race did not appear to contribute to variations in the iron content of the placentas studied, nor did hospital classification, age, weight change during pregnancy, the number of previous pregnancies, fetal weight and maternal hemoglobin prior to delivery.

SUMMARY

Iron content was determined in fifty intact placentas plus cords, but one value, 6 standard deviations from the mean total iron content was omitted from subsequent calculations. Total iron content ranged from 34.5 to 170 mg. and averaged 75.5 mg., while the mean concentration of the mineral was 13.6 mg. and the range 7.1 to 34.8 mg. per 100 gm. of the wet weight of the samples. This loss of iron represented an average of 8.4 per cent, from a 3.5 to 18 percentage range, of a 900 mg. total dietary increment suggested for pregnant women.

REFERENCES

1. Salhanick, H. A., Neal, L. M. and Mahoney, J. P. Blood content of the human placenta. *J. Clin. Endocrinol.*, 16: 1120, 1956.
2. Curtis, R. M. and Worthington, R. W. Placental blood plasma. *Am. J. Obst. & Gynec.*, 42: 428, 1941.
3. Mitchell, F. L. and Davies, R. E. The isolation and estimation of the steroid estrogens in placental tissue. *Biochem. J.*, 56: 690, 1954.
4. Mischel, W. Die anorganischen Bestandterle der Placenta. *Arch. Gynäk*, 190: 638, 1958.
5. Woiwod, A. J. The determination of iron in biological material. *Biochem. J.*, 41: 39, 1947.
6. Food and Nutrition Board: Recommended Dietary Allowances, Revised 1958. National Academy of Sciences, National Research Council Publication No. 589, 1958.

A Longitudinal Study of the Animal Protein Intake of Children from One to Eighteen Years of Age

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MANY studies have contributed to the description of dietary intakes of children. Virtually nothing, however, is known about sequential changes in the food intakes of children as individuals during the years of growth and development. This report is one of a series dealing with the dietary intake data of a group of children followed individually throughout the major portion of their growth period while living at home under varying conditions of everyday life; it deals with the usual food intakes of these children and the various ways in which they changed their nutrient intake patterns during their years of growing up. The 125 children, sixty-four boys and sixty-one girls, whose animal protein intakes are reported here, belong to the Maturity Series of the Longitudinal Studies of Child Health and Development conducted by the Department of Maternal and Child Health, Harvard School of Public Health, under the direction of one of us (H.C.S.). The background of this research project, the methodologies and technics employed in the collection and analysis of the data have already been described.[1] The Burke Research Dietary History Method[2] was used for the collection of the dietary data at each routine visit of the child to the clinic, i.e., semi-annually during the early years and annually thereafter. Detailed nutrition histories were obtained in which the average daily dietary intakes of the preceding time interval were ascertained.

The total caloric and total protein intakes of these children have already been reported.[2] In line with the objectives of future reports from this research project, i.e., to determine relationships between intakes of nutrients and manifestations of health and development, it was considered important to ascertain qualitative as well as quantitative differences in the protein intakes of these children. It is generally accepted that most proteins from animal origin are of higher biologic value than those derived from plants, and in diets in which growth is a factor it has long been considered desirable to provide a relatively high proportion of total protein from animal sources. On the other hand, it is well known that despite the relatively low biologic value of plant pro-

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This paper is No. 8 of the monodisciplinary reports in Series II of the Longitudinal Studies of Child Health and Development, Department of Maternal and Child Health, Harvard School of Public Health, Boston, Massachusetts.

Financial support from the many organizations listed in the introductory paper of this Series[1] made possible the collection of the dietary intake histories on which this study is based. In recent years these studies have been supported by the Research Grants Division of the U. S. Public Health Service and the Nutrition Foundation, Inc.

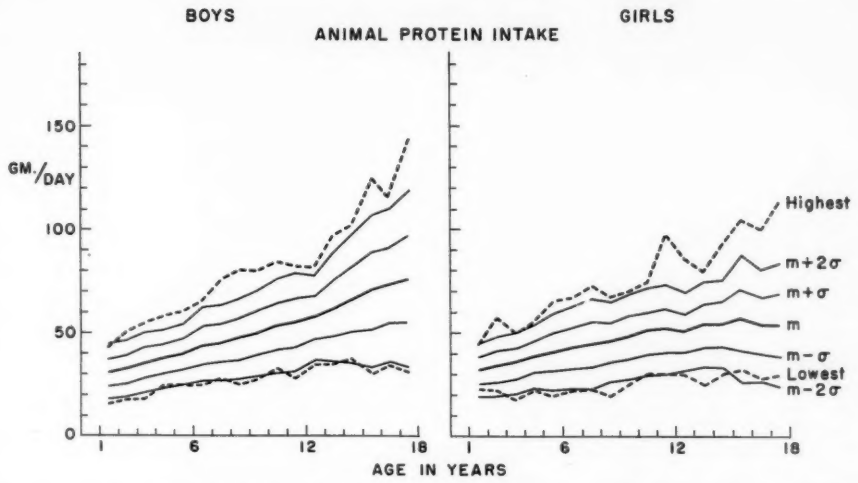


FIG. 1. Animal protein intake of children in the Harvard Longitudinal Studies according to age and sex.

teins mutually supplementary relationships exist when plant foods are combined in the diet whereby deficiencies of essential amino acids in one plant food can be corrected, to some extent at least, by additional amounts of these amino acids from other carefully chosen plant foods. Furthermore, it has been shown that small amounts of animal protein of high biologic value can considerably augment the biologic value of an otherwise vegetarian diet. Research already is concerned with and in the future will show increased interest in the amino acid evaluation of diets in relation to amino acid requirements. However, with the information at present available on the amino acid composition of foods, and the nature of our data, it does not appear practical to attempt detailed evaluation of the diets of these children in terms of their essential amino acid content. With this in mind the amount of animal protein intake was determined. Since both the total and animal protein intakes (grams per day) are known, the amount of protein (grams per day) from plant origin can be obtained by difference.

METHODS

The dietary data covering the entire childhood of these 125 children are based on 2,707 nutrition histories, each history providing a quantitative appraisal of the average daily dietary intake of a child for the preceding six- or twelve-month interval. The total person years of experience represented by the 125 children are 2,125, i.e., a seventeen-year period for each child. The 2,707 histories provide information for approximately 91 per cent of these person years. Estimates of intakes were made by interpolation for the years when histories were not obtained and for the occasional history considered too incomplete to justify inclusion in this analysis. In this way every child was represented in the analysis at every age period. For the description of the procedure used in the estimation of intakes and the use of these estimates the reader is referred to the report on the caloric and protein intakes of these 125 children.[2]

RESULTS

The cross-sectional distribution of the animal protein intakes of the sixty-four boys and sixty-one girls of the Maturity Series of this longitudinal research project is represented by sex and age in Figure 1 and Table 1.

Variations in intake with age and sex are clearly illustrated by the animal protein curves. The average intakes are very similar for the two sexes in the preschool years. During the school years, especially the late school years, the boys display a high rate of increase in intake compared to the girls, resulting in increasingly higher values for the boys in the

TABLE I
Animal Protein Intake (grams per day) According to Age and Sex

Age (yr.)	Boys				Girls			
	Mean	S.D.	Lowest	Highest	Mean	S.D.	Lowest	Highest
1–2	30.6	6.5	15.0	42.5	32.1	6.4	22.5	45.0
2–3	32.5	7.0	17.5	50.0	33.9	7.4	22.5	57.5
3–4	35.7	7.3	17.5	55.0	35.4	7.4	17.0	50.0
4–5	37.7	7.0	25.0	57.5	38.9	7.7	22.0	55.0
5–6	39.8	7.4	25.0	60.0	41.0	9.3	19.0	65.0
6–7	44.0	9.1	25.0	65.0	43.0	9.9	22.5	67.5
7–8	44.9	9.1	27.5	75.0	44.6	10.8	23.0	72.5
8–9	46.8	9.9	25.0	80.0	46.0	9.6	20.0	67.5
9–10	49.9	10.4	27.5	80.0	48.2	10.4	25.0	70.0
10–11	53.4	11.5	32.5	85.0	50.9	11.0	30.0	75.0
11–12	54.9	11.9	27.5	82.5	51.5	11.0	30.0	97.5
12–13	57.3	10.2	35.0	82.5	50.5	9.4	30.0	85.0
13–14	62.2	13.3	35.0	97.5	54.0	10.5	25.0	80.0
14–15	66.3	15.5	37.5	102.5	54.4	10.7	30.0	92.5
15–16	70.3	18.6	30.0	125.0	56.9	15.2	32.5	105.0
16–17	73.4	18.4	35.0	115.0	54.2	13.7	27.5	100.0
17–18	76.0	21.0	30.0	142.5	53.8	14.7	30.0	112.5

S.D. = Standard deviation.

later years. The boys' animal protein intakes were highest at eighteen years of age when the average value was 76 gm. per day, the girls reached their maximum, 57 gm. per day, during the fifteen- to sixteen-year period.

Widdowson,[3] in her cross-sectional study of individual children's diets, investigated the average animal protein intakes of children between the ages of one and eighteen years. Insofar as we know, no other equally comprehensive study of animal protein in children's diets exists in the literature. A comparison of her values with those of our Maturity Series shows that our values for animal protein, both for boys and for girls, are always appreciably higher than those of the British children. Except for a few age periods the Boston children also displayed higher total protein intakes than the British children.[2]

The wide range encountered in the total caloric and total protein intakes of these individual children is shown also by the animal protein values. In Widdowson's group similar individual variation is in evidence. In the Boston group at every age period, among the boys as well as the girls, the child with the highest intake consumed at least twice as much animal protein as the child with the lowest intake. At every age, one to eighteen years, and for both sexes there was at least one child whose animal protein intake was actually lower than the maximum intake at one year of age.

It was not always the same children who occupied these extreme positions. Although some children maintained the highest or lowest positions for only two or three consecutive years, the intake of one boy ranked highest for eleven different age periods. Figure 1 gives a cross-sectional picture of the animal protein intakes and progressive changes in intakes of the boys and girls in this series during their years of growing up. It does not, however, show how individual children deviate from their average pattern of change in intake.

In order to make it possible to view the data longitudinally in terms of individual patterns of consumption of animal protein, the children were classified according to their levels during three broad age periods (one to six, six to twelve, and twelve to eighteen years). Within each age interval the cumulative intake of animal protein was calculated for each boy and girl, and these values were grouped into quartiles for each sex. Children ranking in

TABLE II
Cumulative Values of Animal Protein Intake Which Define the Extreme Quartiles by Sex and Age Intervals

Age (yr.)	Gram per Day							
	Boys				Girls			
	Lowest Value	25th Percentile	75th Percentile	Highest Value	Lowest Value	25th Percentile	75th Percentile	Highest Value
1–6	115.0	156.2	191.9	262.5	111.0	160.0	207.5	272.2
6–12	172.5	259.4	326.2	467.5	166.8	241.9	322.5	385.0
12–18	210.0	348.0	443.8	640.0	210.0	283.5	357.5	530.0
1–18	615.0	772.5	957.5	1,370.0	487.8	696.2	876.4	1,082.5

TABLE III
Frequency of Occurrence of Individual Longitudinal Patterns of Animal Protein Intake

Patterns	No. of Boys	No. of Girls
HHH	5	5
MMM	12	12
LLL	6	4
MLL, HLL, HMM	(2 + 0 + 5) = 7	(1 + 1 + 2) = 4
LMM, LHH, MHH	(2 + 0 + 3) = 5	(2 + 0 + 3) = 5
MML, HHL, HHM	(2 + 1 + 3) = 6	(7 + 0 + 4) = 11
LLM, LLH, MMH	(3 + 0 + 4) = 7	(5 + 1 + 2) = 8
LML, LHL, LHM, MHL, MHM	(4 + 0 + 0 + 1 + 3) = 8	(2 + 0 + 0 + 0 + 3) = 5
MLM, MLH, HLM, HLH, HMH	(4 + 1 + 0 + 0 + 2) = 7	(3 + 0 + 0 + 0 + 3) = 6
LMH	1	1
HML	0	0

H—High; M—Medium; L—Low.

the lowest quartile of the distribution were classified as having a "low" (L) value, those in the highest quartile as having a "high" (H) value, and those that fell between the 25th and 75th percentiles were classified as "medium" (M) value in intakes. The values defining the extreme quartiles are given in Table II.

For the one- to eighteen-year period each child was assigned a pattern according to the combination of his ratings in the three age intervals. For example, Boy 139 (Fig. 2) was among the sixteen boys who for the one- to six-year interval had the lowest cumulative values of the group, but this boy increased his intake rapidly so that for the six- to twelve-year interval his intake rated "medium" and for the twelve- to eighteen-year interval his cumulative value ranked in the highest quartile of the distribution. Therefore, his pattern of intake was classified as "consistently rising" (LMH).

According to this method of classification there were twenty-seven possible patterns. On the basis of direction of change in intake from one interval to the other these twenty-seven patterns were combined into eleven pattern groups. The distribution of the sixty-four boys and sixty-one girls in the different patterns and pattern groups is shown in Table III.

Figures 2 and 3 illustrate differences as well as similarities between patterns and pattern groups and between children in the same pattern or pattern group. For example, boys in the "consistently low," "consistently medium" and "consistently high" groups conform more or less to the average pattern of the series in the rate at which they change their

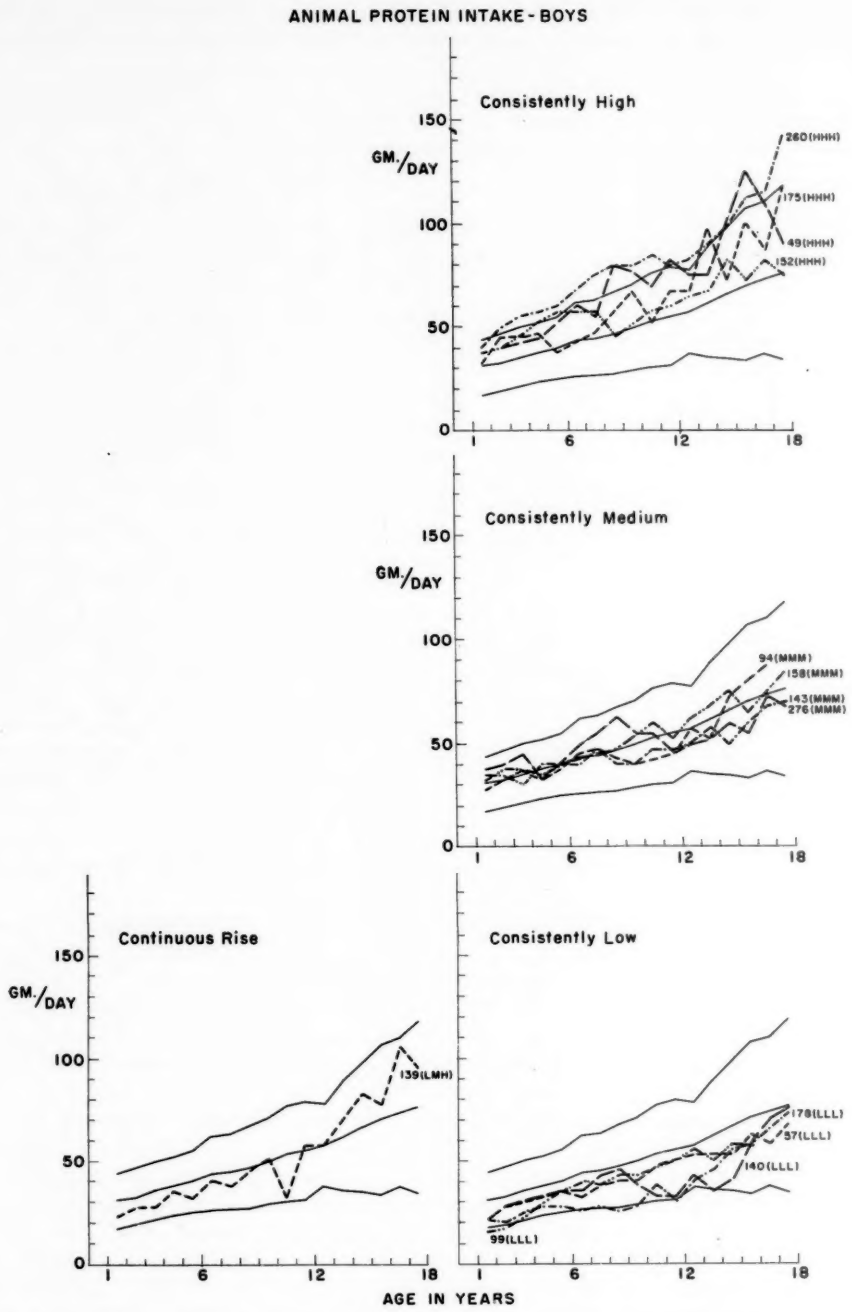
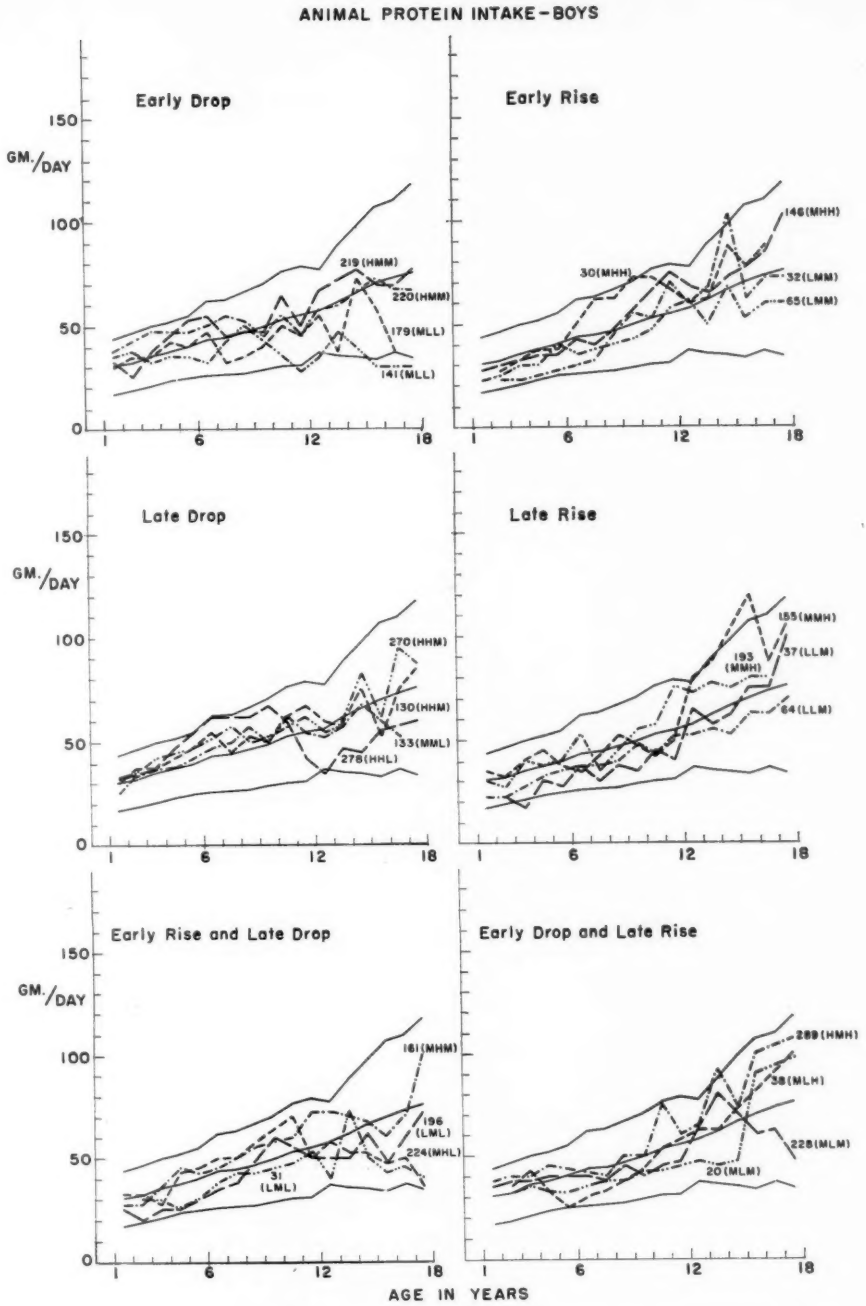


FIG. 2. Selected individual curves of boys' animal protein intake shown in the pattern groups



to which they conform, plotted against the cross-sectional norms for the Maturity Series.

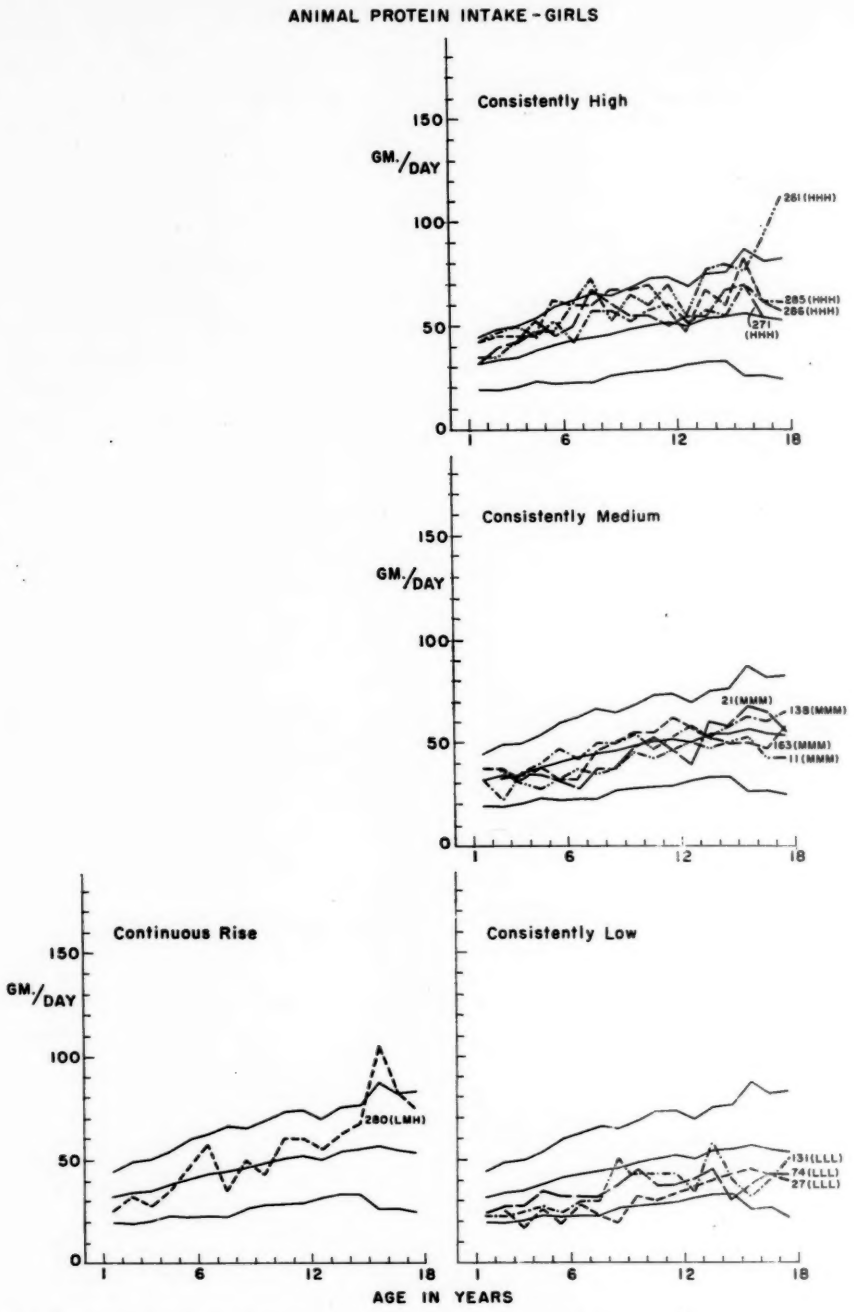
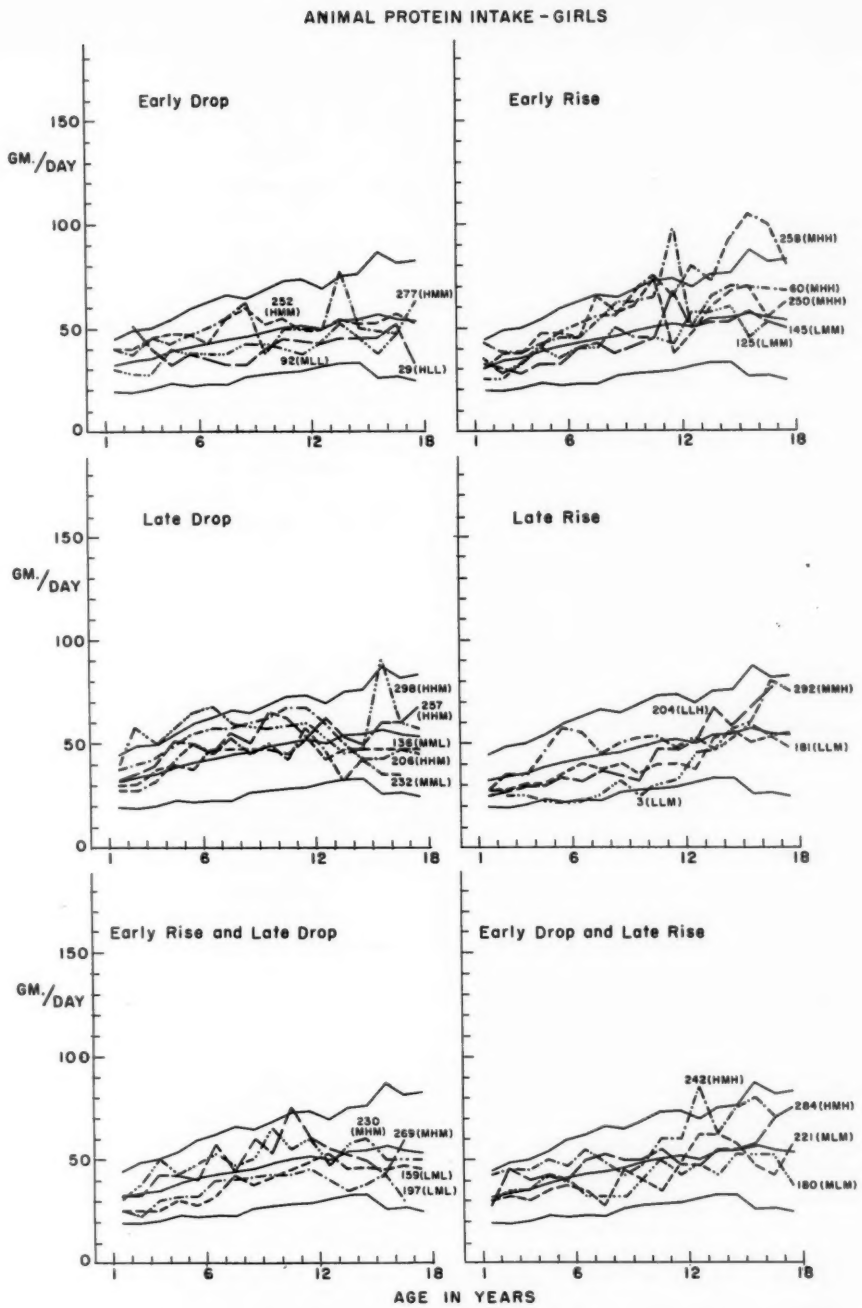


FIG. 3. Selected individual curves of girls' animal protein intake shown in the pattern groups



to which they conform, plotted against the cross-sectional norms for the Maturity Series.

intakes with age, but display a wide range in level of intake with many intermediate variations between extremes of over-all intake as presented in Cases 178 (LLL) and 260 (HHH) in the "consistently low" and "consistently high" categories, respectively. The boys in the other pattern groups show widely different patterns of change in intake. There are differences in direction of change, see, for example, Case 220 (HMM) in the "early drop" category in contrast to Case 146 (MHH) in the "early rise" category and Case 133 (MML) in the "late drop" versus Case 37 (LLM) "late rise" category or Case 224 (MHL) versus Case No. 38 (MLH). There are also differences in the timing of change; compare, for example, Cases 141 (MLL) and 133 (MML), respectively, in the "early drop" and "late drop" categories. Differences in amount of change are well illustrated by cases in the rise and drop categories; compare, for example, the intake in Case 278 (HHL) with the intakes in Cases 270 (HHM) and 130 (HHM).

The gradations of difference in levels and in direction and rate of change within patterns and pattern groups as well as between different pattern groups should be noted. In the "consistently medium" category, for example, there is a relatively high over-all animal protein intake in Case 138 (MMM) in relation to Case 11 (MMM). In level of intake Case 11 occupies an intermediate position between Case 138 (MMM) and Case 74 (LLL) which falls in the "consistently low" category.

In Case 21 (MMM), also in the "consistently medium" category, there is a lower over-all level of intake than in Case 138 (MMM), but this child proceeds with a comparatively rapid increase in intake, particularly in the later years, from a relatively low intake in the one- to six-year interval to a relatively high intake in the twelve- to eighteen-year interval. Thus, with regard to pattern of change, Case 21 (MMM) tends to occupy an intermediate position between Case 138, also in the "medium category," and children in a rising category such as Case 3 (LLM) in the "late rise" and Case 145 (LMM) in the "early rise" category.

SUMMARY

The cross-sectional distributions of the animal protein intakes of sixty-four boys and sixty-one girls of the Maturity Series of this longitudinal research are described for the age period one to eighteen years. Wide variations in intake with age and sex are clearly shown. The average intakes are very similar for the two sexes in the preschool years. During the school years, especially the late school years, the boys displayed a high rate of increase compared to the girls. The boys' animal protein intakes were highest at eighteen years of age, when the average value was 76 gm. per day; the girls reached their maximum, 57 gm. per day, during the fifteen- to sixteen-year interval.

A comparison with Widdowson's cross-sectional values for animal protein shows that our values are always appreciably higher than those for the British children.

In order to view our data longitudinally in terms of individual patterns of consumption of animal protein, the boys and girls in the Maturity Series were classified according to their levels of intake into pattern groups by a procedure described in the text, using values for cumulative intakes of animal protein within specified age intervals. The frequency of occurrence of the individual longitudinal patterns of animal protein intake are presented in the tables, and the figures show the gradation of difference in levels of animal protein intake as well as in the direction and rate of change within patterns and between pattern groups.

REFERENCES

1. Stuart, H. C. and Reed, R. B. et al. Longitudinal studies of child health and development, Harvard School of Public Health, series II, no. 1. Description of project. *Pediatrics*, 24: 875, 1959.
2. Burke, B. S., Reed, R. B., van den Berg, A. S. and Stuart, H. C. Longitudinal studies of child health and development, Harvard School of Public Health, series II, no. 4. Caloric and protein intakes of children between one and eighteen years of age. *Pediatrics*, 24: 922, 1959.
3. Widdowson, E. M. A study of individual children's diets. Medical Research Council, Special Report, series no. 257. London, 1947. H. M. Stationery Office.

Lysine Supplementation of a Rice and Milk Diet Fed to Children Recovering from Kwashiorkor and Undernutrition

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DIETS consumed by a majority of the population in Ceylon are deficient in calories and in proteins,[1–3] especially protein of high biologic value. The staple food in Ceylon is rice which, like most cereals, is relatively deficient in some indispensable amino acids, chiefly lysine.[4,5] While there is a large volume of evidence to indicate that supplementation of wheat flour with lysine results in a product of increased biologic value,[6–8] similar supplementation of other cereal foods has yielded equivocal results. Zein, even when supplemented with theoretically adequate levels of the essential amino acids in which it is deficient, does not support optimum growth of rats.[9–11] A slight but significant improvement in white rice has been reported when it is supplemented with methionine,[12] with lysine[12,13] and with lysine and threonine[5]; in many of these experiments, however, the diets contained purified constituents or consisted primarily of one staple food, for example, rice. Baptist and de Mel,[14] on the other hand, found that a rice and legume diet was capable of supporting growth in healthy children, but the rate of growth in rats maintained on similar diets has been slower and smaller than in those on a stock diet.[15,16] Gomez and co-workers[17] found that the absorption of nitrogen from a diet of maize and beans by children suffering from kwashiorkor was low, but could be significantly increased by the addition of milk. Albanese et al.,[18] on the other hand, found it was necessary to add lysine to a diet consisting mainly of milk to bring about optimal growth.

This is a report of the results of a study of lysine supplementation of a diet fed to children between the ages of nine months and two years recovering from general undernutrition and from kwashiorkor at the Lady Ridgeway Children's Hospital, Colombo, Ceylon, during the period June 1957 to February 1958. The problem of supplementation of rice diets consumed by children in Ceylon is briefly discussed.

EXPERIMENTAL STUDIES

The differentiation between general undernutrition and kwashiorkor was made on criteria described previously.[19] As far as possible children of similar age were selected for the different groups. Eight children recovering from general undernutrition were divided into two groups, one to be given lysine (group 1), the other (group 2) being kept as controls. Owing to an insufficiency of numbers, all patients recovering from kwashiorkor (a total of five) were grouped together (group 3) and given the supplement.

Each child was treated for one to three weeks until the clinical condition improved, and was then given a diet consisting of some milk and fruit (see Table 1). After a period of thirty days on this diet (period 1) lysine in the form of L-lysine hydrochloride (supplied by

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TABLE I
Plan of Diet Fed to the Children

Morning meal
Milk
Bread and butter
Mid-morning drink
Orange juice
Lunch
Rice, leafy vegetable,* other vegetable† or milk with rusks or bread
Banana
Afternoon tea
Bread or rusks with banana
Dinner
As for lunch
Late night drink
Malted milk

NOTE: The vegetables are cooked in coconut milk which is obtained by mixing finely grated coconut kernel with water and expressing the "milk" by hand. The cooked "milk" was also served as gravy. During experimental period 2, lysine (50 mg. of L-lysine hydrochloride per lb. body weight) was given with the milk fed to children in groups 1 and 3.

* One of the following: mukunuwenna (Alternanthera triandra), spinach (Basella alba), tampala (Amaranthus var.), agati leaf (Sesbania grandiflora).

† One of the following: lentil (Lens esculenta), ash plantain (Musa sepientum), snake gourd (Trichosanthes anguina), okra (Hibiscus esculentus).

the E. I. du Pont de Nemours Co., Inc.) was added to the diet of groups 1 and 3 (50 mg. per pound body weight of the hydrochloride being mixed with the milk each day). The administration of lysine was discontinued after thirty days (period 2) and the unsupplemented diet was then given to all three groups for a further period of thirty days (period 3). The children were allowed to eat as much as they desired and the amount of food consumed was measured. Vitamin supplements were given to all the children throughout the experiment.

At weekly intervals a clinical assessment of each child was made, measurements of height, weight and thickness of subcutaneous tissue were taken, and blood was drawn for the estimation of plasma proteins.

Subcutaneous Tissue Measurement

A pair of Harpendon skinfold calipers (British Indicators, Ltd.) recommended by Edwards et al.[20] was used, the readings being taken by the same observer on all the children throughout the experiment. Two readings were recorded over the inferior angle of scapula on each side at minute intervals and the mean value regarded as a criterion of fatness.

Plasma Proteins

Heparinised venous blood was centrifuged, the proteins in 0.2 ml. of the separated plasma were precipitated with tungstic acid, and the nitrogen was estimated by the microKjeldhal method. The plasma proteins were fractionated by filter paper electrophoresis using Whatman No. 1 filter paper strips (3 cm. by 25 cm., previously soaked in 1 per cent sodium citrate and dried) and veronal buffer, pH 8.6, a voltage of 110 volts being applied for sixteen hours. The dried paper was stained in amido-black 10B,[21] rendered translucent and scanned in densitometer.

The phospholipids in plasma were estimated in a few cases by the extraction of a trichloracetic acid precipitate of the plasma with an ethanol-chloroform-ether mixture previously used.[22]

RESULTS

During the latter half of the third experimental period three children contracted measles, two had infective diarrhoea and one acute bronchitis. Therefore, the data obtained during the last thirty days of the experiment are not presented.

Food Consumption

The weights of cooked foods consumed were converted to dry weight and the calorie and protein content calculated from published data.[23] The lysine and threonine contents of the proteins were estimated from values published by Block and Weiss.[24]

During the course of the experiment the children were gradually weaned from the almost total milk diet given for the intiation of cure to one containing bread, rice and vegetables as well as milk. They were encouraged to eat as much rice or bread as possible before the milk was offered them. The amount of calories, proteins, lysine and threonine derived from the diet by the children in the different experimental groups during the four weeks preceding (period 1) and during the supple-

TABLE II

Average Daily Intake (per kg. Body Weight) of Calories, Proteins, Lysine, and Threonine, and the Change in Body Weight (as gm. per Day) of the Children During the Four Weeks Immediately Preceding (Period 1) and During (Period 2) Lysine Supplementation

Group	Period	Calories	Proteins (gm.)	Lysine (mg.)	Threonine (mg.)	Change in Body Weight (gm. per day)
1	1	58	2.7	183	123	36
	2	67	2.5	154	101	24
2	1	57	2.6	169	114	32
	2	63	2.0	107	76	27
3A	1	61	3.1	204	137	25
	2	72	2.4	156	98	22
3B	1	63	2.2	183	95	− 7
	2	74	1.9	121	79	28

mentation of the diet with lysine (period 2) is given in Table II. The amount of food consumed varied considerably among the different subjects and also in the same subject during different weeks. There was a slight drop in food consumption during the first week of lysine supplementation in many cases, but these children soon recovered their appetite as supplementation was continued. The addition of lysine did not result in a marked improvement in appetite as noticed by Albanese et al.[18]

The calorie intakes were well below the value of 110 calories per kg. body weight recommended for children between six months and three years of age,[25] and agree with the values obtained by Pretorius and Smit[26] during the treatment of patients with kwashiorkor. The protein intakes were in accord with values of 2.2 and 3 gm. per kg. body weight suggested by György and by Holt.[27,28] The amounts of lysine and threonine taken by these convalescent children, who were replenishing depleted tissues, were equal to those recommended by Albanese[8] for normal children. Our results indicate that the amounts recommended by Pratt[29] and by Holt and Snyderman,[30] namely, 90 mg. lysine and 60 mg. threonine per kg. body weight, are more likely to represent the requirements of normal children in this age group.

Growth

The change in body weight of the children during the first two experimental periods is shown in Table II. The group of patients with kwashiorkor has been sub-divided into groups 3A and 3B as two of these subjects showed an increased rate of growth during period 2.

The rate of change of body weight and of "body fat" (as measured by the calipers) was not increased by lysine supplementation. The rates in groups 1 and 3A were similar to those for group 2 which received no supplement. Only the two children in group 3B grew more rapidly during lysine supplementation than before. It is possible that the fall in weight of these children during period 1 was due to the continued loss of water from the tissues during recovery from acute kwashiorkor, even though no oedema was apparent clinically at the commencement of the experiment. This was borne out by corresponding changes in the subcutaneous tissue measurement.

Measurement of subcutaneous tissue has been widely used in the assessment of human nutrition;[31] measurement over several sites is recommended: the triceps, subscapular and the supra-iliac sites[20] being considered to give the most accurate assessment of subcutaneous fat in any person at a given time. However, measurement over the same site during successive periods of time gives a reliable indication of a change in the rate of growth, as shown by results obtained in this experiment and also by valves obtained on healthy children of the same age group.[32] Changes in subcutaneous tissue measurement in general paralleled changes in body weight, a fall in weight being accompanied by a decrease in the reading.

TABLE III
Plasma Protein Concentrations (in gm. per 100 ml.) During the Three Weeks Prior to and During Lysine Supplementation of the Diet

Group	Period	Total Protein	Albumin	Alpha$_1$-globulin	Alpha$_2$-globulin	Beta-globulin	Fibrinogen plus Gamma Globulin	Albumin: Globulin Ratio
1	1	5.78	2.81	0.21	0.62	0.67	1.53	0.99
	2	6.39	3.34	0.18	0.59	0.78	1.48	1.10
2	1	5.63	2.70	0.20	0.55	0.59	1.64	0.97
	2	6.44	3.15	0.23	0.60	0.72	1.75	0.98
3A	1	6.31	3.44	0.19	0.54	0.69	1.74	0.99
	2	6.64	3.50	0.16	0.70	0.64	1.77	1.15
3B	1	5.92	3.00	0.25	0.49	0.60	1.60	1.04
	2	6.37	3.20	0.21	0.61	0.83	1.56	1.01

NOTE: Three estimations were made on each child during each experimental period.

Plasma Proteins

The concentration of proteins in blood plasma also gives an indication of the state of nutrition of an individual.[31] The results obtained in this experiment are given in Table III. The values obtained during the three weeks preceding lysine supplementation and during the first three weeks of period 2 have been averaged for each child and the mean for the group obtained.

During period 1 the total proteins and the albumin fraction increased rapidly in all the groups, but the rate of increase diminished markedly in period 2. The changes in groups 1 and 3 must be due to a gradual return of the child to normality and not to the administration of lysine, as similar changes were seen in group 2. The other protein fractions showed no marked change during the experiment. No significant fall in the alpha-globulin level was seen with recovery from kwashiorkor, as has been reported by others,[33,34] probably due to the fact that the children had recovered from the acute stage before they were selected for the experiment.[35]

There was an initial rise in plasma phospholipids in patients with kwashiorkor and in those with general undernutrition. The mean value for phospholipid phosphorus per 100 milliliters plasma fell from 13.4 mg. at the start of the experiment to 8.3 mg. at the beginning of period 2 and was 7.4 mg. at the beginning of period 3. Similar changes in serum bound lipids have been reported by Dean and Schwartz[36] in patients with kwashiorkor and are likely to be due to a sudden increase in the rate of growth which had been halted under the stress of malnutrition.[37] Lysine supplementation had no effect on serum phospholipids.

COMMENTS

The number of children in each group is too small for a statistical analysis of the results. From our data, however, it may be concluded that the addition of lysine to the diet fed to these children did not bring about an increased rate of growth. The children maintained a steady improvement in weight gain during the experimental periods, and the rate of growth of those given lysine was similar to that of the group receiving the unsupplemented diet. Clinically, too, there was a marked improvement in the condition of the children in all groups during the course of the experiment, despite a low colorie intake; when discharged from the hospital they looked as fit and healthy as children of similar age and economic status. This is in marked contrast to the results obtained by Albanese and co-workers,[18] who also used a diet containing a high proportion of milk, and in agreement with the findings of Gaitonde et al.[38]

The ratio of lysine to threonine in the diets of these children varied from 1.4 to 1.5, which agrees with the value of 1.3 considered optimal for the rat.[39] During the period of lysine supplementation, however, this ratio ranged from 2.0 to 2.6 in groups 1 and 3, and yet the

children showed no effects of an amino acid imbalance;[40] the slight decrease in the rate of growth brought about by the addition of lysine in groups 1 and 3A (Table II) is not significant. Gaitonde et al.[38] obtained a more marked effect on adding lysine to the diet of patients with kwashiorkor, the average weight gain being 1.3 pounds during the three weeks of their experiment as compared with 3.2 pounds gained by the control group. Details of their "hospital diet" are not given.

That a mixture of amino acids rather than one amino acid is necessary to correct the deficiencies of a diet of highly polished rice has been established.[39,41,42] If such supplementation is to be effective in human nutrition the amino acids must be mixed with the whole grain and the grain then coated with a water-insoluble but digestible substance, as was done during the enrichment of rice with vitamins in the Phillipines,[43] to resist the effect of excessive washing of rice prior to cooking. Such a procedure will make amino acid supplementation very uneconomical. A more practical way of improving the value of a rice diet is to supplement it with foods containing well balanced proteins[42] or with proteins that can supply the deficiencies in the rice protein. Milk, although an excellent supplement, is scarce and expensive in underdeveloped countries, and deteriorates rapidly due to lack of effective refrigeration. Beef is cheaper but it is taboo to both Hindu and Buddhist. Of the various food supplements suggested[44] the following could be used in Ceylon: pulses, green leafy vegetables, fish and coconut.

Pulses

Several reports indicate the importance of pulses in the diets of pre-school and older children.[14,45–47] The most popular pulse in Ceylon is lentil (Lens esculenta); this is well tolerated by children provided it is well boiled. A relatively small amount can contribute substantially to the protein content of the diet. Unfortunately it is not grown in Ceylon, nearly all that is consumed being imported from India.

Leafy Vegetables

Although the protein content of green leaves is low, the protein is of a high biological value,[24] and green vegetables have been used successfully in supplementing rice diets.[48]

Fish

Fish is the one animal food that is acceptable to a large majority of the population. Sea fish is popular but the supply is insufficient, the prices high and the distribution largely confined to coastal districts. Only a few varieties of fresh water fish are eaten, and the supply is negligible. Fish, salted and dried, is commonly consumed in small quantities. The consumption of fresh water fish could be popularised, especially by breeding the more acceptable varieties in inland tanks and rivers and in rice fields during the period of inundation, as is done in Japan. Fish that is not popularly eaten when fresh could be either converted to fish meal or salted and dried.

Coconut

The residue left after extraction of the oil from the kernel has a high content of good quality protein, but its high fibre content makes it unsuitable for liberal use in the diets of young children. The production of a refined flour from coconut is at present engaging the attention of the Ceylon Institute for Scientific and Industrial Research, and it is hoped that the product will be suitable for addition to milk. It could be mixed with foods like manioc powder and fish meal. At present coconut is used in cooking in the form of "milk": the finely grated kernel is mixed with water and the "milk" expressed by hand, the process being repeated twice. Up to 80 per cent of the protein and most of the fat in the kernel are present in this milk[14] which is used for cooking vegetable and other curries. The feeding of more vegetables such as lentil and greens cooked in this milk would thus add to the protein in the diet. The milk has also been shown to be useful in the treatment of gastrointestinal disturbances in children.[49]

Increasing the local production of rice would make available more parboiled and lightly milled rice with a higher protein content than the highly milled white rice now imported. The germ and bran removed when polishing

rice is an effective supplement to white rice.[50] Good quality rice, if eaten in sufficient quantity, is apparently capable of keeping the population in positive health.[51]

Since World War II an increasing proportion of the population have taken to eating bread, at least one meal of bread per day being consumed in many homes. Wheat flour could be effectively enriched with several nutrients, including amino acids, provided a larger number of the poorer people could be persuaded to take bread at one of the meals, and the world's surplus of wheat was made available to them at a price within their means.

SUMMARY

Changes in body weight, thickness of subcutaneous tissue and in the concentration of proteins of the plasma have been investigated in five children recovering from kwashiorkor and in four from general undernutrition, prior to and during lysine supplementation of a milk plus rice and bread diet.

No difference in the rate of growth or in the improvement of plasma proteins was found between the two groups, or in the same group when results of the two experimental periods were compared. Nor was a difference noticed between these two groups and a third group of four undernourished children fed the same diet unsupplemented with lysine.

The intake of nutrients per day per kilogram body weight from the diet was as follows: calories 46 to 85, proteins 1.9 to 3.4 gm., lysine 115 to 200 mg. and threonine 77 to 142 mg.

The problem of improving the quality of rice diets fed to Ceylonese children is briefly discussed.

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REFERENCES

1. Nicholls, L. and Nimalasuriya, A. Rural dietary surveys in Ceylon. *Ceylon J. Sc.* (*D*), 5: 59, 1941.
2. Cullumbine, H., Bibile, S. W. and Wikramanayake, T. W. A study of diets of various Ceylon communities. *Ceylon J. M. Sc.* (D), 6: 255, 1949.
3. Clements, F. W. and Bocobo, D. L. Report on nutrition in Ceylon. WHO/57/12/9206, 1958. FAO.
4. Block, R. L. and Bolling, D. Amino-acid Composition of Proteins and Foods; Analytical Methods and Results, 2nd ed. Springfield, Ill., 1951. Charles C Thomas.
5. Pecora, L. J. and Hundley, J. M. Nutritional improvement of white polished rice by the addition of lysine and threonine. *J. Nutrition*, 44: 101, 1951
6. Flodin, N. W. Amino-acids and proteins. Their place in human nutrition problems. *J. Agriculture & Food Chem.*, 1: 222, 1953.
7. Bender, A. E. Nutritive value of bread proteins fortified with amino-acids. *Science*, 126: 874, 1958.
8. Albanese, A. A. Proteins and amino-acid requirements of mammals, p. 115. New York, 1950. Academic Press.
9. Harris, H. A., Neuberger, A. and Sanger, F. Lysine deficiency in young rats. *Biochem. J.*, 37: 508, 1943.
10. Albanese, A. A., Snyderman, S. E., Lein, M., Smetak, E. M. and Vestal, B. The biological value of corn and wheat proteins in the male infant, with a note on the utilisation of D-tryptophan. *J. Nutrition*, 38: 215, 1949.
11. Kliger, D. and Krehl, W. A. Lysine deficiency in rats. *J. Nutrition*, 41: 215, 1950.
12. Kik, M. C. The nutritive value of the proteins of rice and its by-products. I. Effects of amino-acid additions on growth. *Cereal Chem.*, 17: 473, 1940.
13. Rosenberg, H. R. and Culik, R. The improvement of the protein quality of white rice by lysine supplementation. *J. Nutrition*, 63: 477, 1957.
14. Baptist, N. G. and de Mel, B. V. Growth and amino-acid intakes of children on a cereal-legume-vegetable diet. *Brit. J. Nutrition*, 9: 156, 1955.
15. Goettsch, M. Incomplete recovery of the rat after early retardation in growth. *Fed. Proc.*, 11: 444, 1952.
16. Wikramanayak, T. W. and Hoover, G. The rate of growth of rats on various diets. *Ceylon J. M. Sc.* (*D*), 9: 89, 1958.
17. Gomez, F., Ramos-Galvan, R., Cravioto, J., Frenk, S., de La Peña, C., Moreno, M. and Villa, M. E. Protein metabolism in chronic severe malnutrition (kwashiorkor). *Brit. J. Nutrition*, 11: 229, 1957.
18. Albanese, A. A., Higgons, R. A., Hyde, G. M. and Orto, L. Biochemical and nutritional effects of lysine-reinforced diets. *Am. J. Clin. Nutrition*, 3: 121, 1955.
19. de Silva, C. C. Kwashiorkor (protein malnutrition). *Ceylon M. J.*, 3: 55, 1955.

20. Edwards, D. A. W., Hammond, W. H., Healy, M. J. R., Tanner, J. M. and Whitehouse, R. H. Design and accuracy of calipers for measuring subcutaneous tissue thickness. *Brit. J. Nutrition*, 9: 133, 1955.
21. Abdel-Wahab, E. M., Rees, V. H. and Laurence, D. J. R. Evaluation of the A/G ratio of plasma and serum by paper electrophoresis. Ciba Foundation Symposium on Paper Electrophoresis, p. 30. London, 1956. J. & A. Churchill.
22. Wikramanayake, T. W., Munro, H. N., Naismith, D. J. and Hutchison, W. C. A note on the influence of energy intake on phospholipid metabolism. *Biochem. J.*, 55: 640, 1953.
23. Food Consumption Tables for International Use. FAO Nutritional studies No. 11. Rome, Italy, 1954. FAO
24. Block, R. J. and Weiss, K. W. Amino-acid Handbook. Springfield, Ill., 1956. Charles C Thomas.
25. Calorie Requirements: FAO Nutritional Studies No. 15. Rome, Italy, 1957. FAO.
26. Pretorius, P. J. and Smit, Z. M. Effect of various skimmed milk formulae on the diarrhea, nitrogen retention and initiation of cure in kwashiorkor. *J. Trop. Pediat.*, 4: 50, 1958.
27. György, P. and Holt, L. E., Jr. Human Protein requirements and their fulfillment in practice. In: Proceedings of Conference held at Princeton, 1955. Edited by Waterlow, J. C. and Stephen, J. M. L. New York, 1957. FAO, WHO and Josiah Macy, Jr., Foundation.
28. Holt, L. E., Jr. The protein requirements of man and some considerations involved in meeting them. *West African M. J.*, 7: 9, 1958.
29. Pratt, E. L. The amino-acid and protein requirement of infants. *J. A. M. A.*, 164: 408, 1957.
30. Holt, L. E., Jr. and Snyderman, S. E. Some Aspects of Amino-acid Supplementation. Princeton, N. J., 1956. Rutgers University Press.
31. Sinclair, H. M. Assessment of human nutriture. *Vitamins & Hormones*, 6: 101, 1948.
32. Fernando, P. V. D. and Wikramanayake, T. W. Unpublished data.
33. Senecal, J. The treatment and prevention of kwashiorkor in French West Africa. *Annals New York Acad Sc.*, 69: 918, 1958.
34. Baptist, N. G., de Silva, C. C. and Siddique, M. Electrophoretic pattern of plasma proteins in clinically diagnosed cases of kwashiorkor (protein malnutrition) and undernutrition (marasmus) among Ceylonese children. *Brit. J. Nutrition*, 13: 488, 1959.
35. Catzel, P., Theron, J. J. and Pretorius, P. J. The erythrocyte sedimentation rate in kwashiorkor. *J. Trop. Pediat.*, 4: 98, 1958.
36. Dean, R. F. A. and Schwartz, R. The serum chemistry in uncomplicated kwashiorkor. *Brit J. Nutrition*, 7: 131, 1953.
37. Cravioto, J., de La Pña, C. L. and Burgos, G. Fat metabolism in chronic, severe malnutrition: Lipo-proteins in children with kwashiorkor. *Metabolism*, 8: 723, 1959.
38. Gaitonde, B. B., Lewis, R. A., Patel, B. D. and Rao, G. S. Lysine in the treatment of protein malnutrition. *J. Trop. Pediat.*, 4: 143, 1959.
39. Rosenberg, H. R., Culik, R. and Eckart, R. E. Supplementation of rice with lysine and threonine. *Fed. Proc.*, 18: 544, 1959.
40. Elvehjem, C. A. and Harper, A. E. Importance of amino-acid balance in nutrition. *J. A. M. A.*, 158: 655, 1955.
41. Asenjo, C. F. and Goyco, J. A. Effect of supplementing a polished rice and red kidney bean diet with amino-acids. *Fed. Proc.*, 13: 450, 1954.
42 Deshpande, P. D., Harper, A. E., Quiros-Perez f. and Elvejhem, C. A. Further observations on the improvement of polished rice with protein and amino-acid supplements. *J. Nutrition*, 57: 415, 1955.
43. Rice Enrichment in the Phillipines. FAO Nutritional Studies No. 12, Rome, Italy, 1952. FAO.
44. Autret, M. and Van Veen, A. G. Possible sources of proteins for child feeding in underdeveloped countries. *Voeding*, 16: 286, 1955.
45. Dean, R. F. A. Plant proteins in child feeding. M.R.C. Special Reports Series No. 279. London, 1953. Her Majesty's Stationery Office.
46. Holmans, K. and Lambrechts, A. Nitrogen metabolism and fat absorption in malnutrition and kwashiorkor. *J. Nutrition*, 56: 477, 1955.
47. Gopalan, C. Malnutrition among infants and young children in India. *J. Trop. Pediat.*, 3: 3, 1957.
48. Sur, B. K. Supplementary value of leaves to the poor rice diet. *Bull. Central Food Technol. Res. Inst., Mysore*, 4: 159, 1955.
49. Gesteira, M. and Bahia, A. Oleite de coco nos disturbios nutritivos do lactente. *Brazil med.*, 46: 173, 1932.
50. Kik, M. C. Nutritive value of the protein of rice germ. *Fed Proc.*, 17: 463, 1954.
51. Koblenzer, P. J. The health of the Rungus Dusum of British North Borneo. *J. Trop. M. Hyg.*, 61: 293, 1958.

A Controlled Clinical Comparison of Benzphetamine and D-Amphetamine in the Management of Obesity

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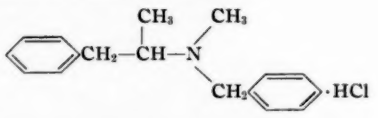
BENZPHETAMINE (Didrex®) is a new anorexic drug which, it is hoped, will serve as a useful adjuvant in the management of obese patients. In a clinical study utilizing the double blind technic, we previously reported the clear statistically significant superiority of benzphetamine over placebo medication in the weight loss achieved by obese outpatients receiving these medicaments for a period of twenty weeks.[1] These results have been amply confirmed in subsequent publications by other clinical investigators.[2–5] The purpose of the present report is to present the results of a follow-up study comparing the efficacy of benzphetamine and d-amphetamine in promoting weight loss in another group of obese outpatients for a period of twenty weeks. The present study also employed the double blind method.

MATERIALS AND METHODS

Benzphetamine or (+) N-benzyl-N,a-dimethylphenethylamine hydrochloride has the following structural formula (dextro form):



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It was synthesized in the laboratories of The Upjohn Company. The pertinent laboratory data concerning the animal pharmacology and the human pharmacology of this compound were presented in detail in our previous publication.[1]

The patients who participated in this study attended the obesity clinic at the Cedars of Lebanon Hospital, Los Angeles. Details concerning them are shown in Table I. It can be seen that the makeup of the patients in both drug-treated groups was about the same. All the patients were under our care. They were subjected to the same weight reduction program with respect to diet, frequency of visits to the clinic and method in which the drugs were administered. The only major variables consisted of the drug dispensed, benzphetamine or d-amphetamine, and the supervising physician (either B. S. or L. W.). A 1,000 calorie, high protein diet was prescribed for each patient. The diet contained 100 gm. of carbohydrate, 84 gm. of protein, and 30 gm. of fat.

The study was performed by the double blind technic using the coded tablets No. 68 and No. 69, which were identical in appearance. Alternate, unselected patients were assigned first to one physician and then to the other. Alternate patients assigned to each doctor were then given the No. 68 and No. 69 tablets in turn. The patients were told to take one of these tablets fifteen minutes before each meal. In the event that weight loss was unsatisfactory, the dose was increased to two tablets before each meal. All in all, twenty patients were started on No. 68 tablets and nineteen on those labeled No. 69. Each patient was seen weekly for four weeks and then once every two weeks for a maximum of twenty weeks. Each patient continued either on the No. 68 tablet or the No. 69 tablet from the beginning to the end of the investigation. At the conclusion of this study, we were informed that the No. 68 tablets were benzphetamine and contained 40 mg. of drug per tablet, and that the No. 69

TABLE I
Patients Studied

Medication	No. of Patients	Mean Age (yr.)	Sex	Mean Weight (lb.)	Mean Overweight (%)
Benzphetamine	20	54	All F	188	53
d-Amphetamine	19	53	18 F, 1 M	190	56

tablets were d-amphetamine and contained 5 mg. of drug per tablet.

The degree of weight loss was expressed as the average pounds lost per patient, the average pounds lost per patient per week and the average performance index per patient. The performance index (P.I.) of a patient, according to the formula of Jolliffe and Alpert,[6] is the actual weight loss over the predicted or hoped-for weight loss times 100. A perfect performance index is 100 per cent, and values less than 100 per cent indicate the approximate degree of the patient's adherence to the dietary program. Use of the performance index eliminates several possible variables by permitting comparison between persons of different sexes, ages, occupations, activities, weights and degrees of obesity.

RESULTS

The results of the study in terms of weight loss have been summarized in Tables II, III and IV. Table II shows the over-all weight loss for the entire duration of the study expressed as total pounds lost, pounds lost per week and total performance index. It is apparent from inspection of this table that there was no difference in the weight loss achieved by patients receiving benzphetamine or d-amphetamine. The slightly greater total weight loss of the patients receiving benzphetamine (15.78 pounds) compared with that of the patients receiving d-amphetamine (13.57 pounds) was not statistically significant ($t = 0.7$). The mean weight loss per week of the patients in both drug groups is comparable to that reported in the previous literature for d-amphetamine and other amphetamine drugs. Furthermore, this weight loss significantly exceeds the weight loss exhibited by groups receiving placebos in two previous double blind studies conducted by us in the same clinic, with the same methodologic format, and with patients of similar composition in terms of age,

TABLE II
Double Blind Study Results in Patients Followed Up Eight Weeks or Longer

Medication	No. of Patients	Weeks Observed	Total Pounds Lost	Pounds Lost Per Week	Total Performance Index (%)
Benzphetamine	19	16	15.78 ± 2.91*	0.98 ± 0.14	36 ± 5.29
d-Amphetamine	17	15	13.57 ± 1.42	1.00 ± 0.12	37 ± 4.16

* Mean and standard error of the mean.

TABLE III
Performance Index at Four-Week Intervals

Medication	Four-Week Periods				
	1	2	3	4	5
Benzphetamine	66 ± 7.87* (20)	32 ± 5.11 (19)	25 ± 8.52 (16)	19 ± 6.89 (14)	17 ± 7.53 (9)
d-Amphetamine	52 ± 6.99 (19)	34 ± 4.52 (17)	21 ± 4.61 (12)	20 ± 9.90 (11)	9 ± 8.69 (8)

NOTE: Figures in parentheses indicate the number of patients.
* Mean (%) and standard error of the mean.

TABLE IV
Pounds Lost Per Week at Four-Week Intervals

Medication	Four-Week Period				
	1	2	3	4	5
Benzphetamine.....	1.84 ± 0.23* (20)	0.86 ± 0.11 (19)	0.70 ± 0.24 (16)	0.49 ± 0.20 (14)	0.53 ± 0.23 (9)
d-Amphetamine.....	1.53 ± 0.16 (19)	0.93 ± 0.16 (17)	0.56 ± 0.14 (12)	0.54 ± 0.24 (11)	0.29 ± 0.25 (8)

NOTE: Figures in parentheses represent the number of patients.
* Mean (lb.) and standard error of the mean.

TABLE V
Similarity of Benzphetamine Results in Two Separate Double Blind Studies

Benzphetamine Study	Total Pounds Lost	Pounds Lost Per Week	Total Performance Index (%)	Pounds Lost Per Week At Four-Week Intervals				
				1	2	3	4	5
First study.....	16.01	0.90	32	1.60	0.83	0.73	0.78	0.43
Second study.....	15.78	0.98	36	1.84	0.86	0.70	0.49	0.53

sex and percentage overweight.[1,7] The weight loss in the groups receiving placebos was 0.28 pound per week[1] and 0.58 pound per week,[7] respectively.

Tables III and IV show the weight loss at four-week intervals. Again, it can be seen that there was no difference in the weight loss achieved by the patients treated with benzphetamine or d-amphetamine. The somewhat greater weight loss exhibited by those receiving benzphetamine during the first and fifth four-week periods was not statistically significant. The weight loss for patients in both drug groups was greatest during the first four weeks of the study. In the ensuing sixteen weeks the patients receiving both drugs maintained a persistent significant weight loss except for those receiving d-amphetamine in the fifth four-week period, at which time the weight loss of this group was negligible. This effect of time on the rate of weight loss is similar to results previously published by us in two previous double blind studies of this type.[1,7]

Table V shows the results of weight loss achieved by patients treated with benzphetamine in two different double blind studies conducted approximately one year apart. The first study, previously reported by us, was a double blind study comparing patients treated with benzphetamine with patients treated with placebos.[1] These patients received doses of benzphetamine ranging from 25 to 50 mg. three times daily. The present study was conducted in the same manner except that patients receiving benzphetamine were compared with those rceceiving d-amphetamine. The dose of benzphetamine used in this study varied from 40 to 80 mg. three times daily. Inspection of the table reveals that the weight loss achieved by patients treated with benzphetamine in both studies was practically identical. The small differences between the two studies in the first and fourth four-week periods are not statistically significant. The data contained in this table illustrate two points. First, no further improvement in weight loss was induced by employing doses of benzphetamine greater than 25 to 50 mg. three times daily. Second, these data attest to the reproducibility of the findings achieved by the methodology employed in these two studies.

Table VI lists the side effects reported. No

TABLE VI
Side Effects Reported During This Study

Symptoms	Benzphetamine	d-Amphetamine
Gastrointestinal symptoms	5	5
Dizziness	4	2
Constipation	2	3
Nervousness and poor sleep	5	6
Pruritus	1	1
Dryness or soreness of mouth	3	3
Chest pain	1	1
Headache	1	4
Malaise	1	2
Fatigue	1	5
Poor appetite control	1	3

attempt was made to grade the severity of these side effects, since they were basically subjective in nature. These side effects were culled from complaints made by the patients at any time during the tenure of the twenty-week study. The side effects exhibited by the patients receiving benzphetamine and d-amphetamine were generally similar, with the following exceptions. The patients receiving benzphetamine complained of dizziness a little more frequently than those receiving the other drugs. On the other hand, the patients receiving d-amphetamine complained more of headache, malaise and fatigue.

COMMENTS

In this double blind study, the weight loss achieved by patients treated with benzphetamine and d-amphetamine was identical. The average weight loss of 1 pound per week over a fifteen- to sixteen-week period, achieved by the patients in both drug groups, compares favorably with rates of loss recorded in the literature for other anorexic agents. Studies on the efficacy of various amphetamine drugs have generally indicated average weight losses varying from 1 to 2 pounds per week over varying periods of time. In terms of potency, this study would indicate that 40 to 80 mg. of benzphetamine taken three times daily is equivalent to a dose of 5 to 10 mg. of d-amphetamine taken three times daily. If the results of a previous double blind study performed by us comparing benzphetamine with placebos (Table v) can be interpolated here, the statement can then be made that 25 to 50 mg. of benzphetamine is equivalent to 5 to 10 mg. of d-amphetamine in potency. In this connection, data published by Oster and Medlar,[2] Schapiro and Bográn[3] and Rhoades suggest that doses of benzphetamine of 50 to 100 mg. daily may be as effective as higher doses of this drug, 150 mg. daily. However, these observations at the present time must be considered suggestive since they are not statistically definitive.

At this writing, there is only one other published study in which the relative anorexic potency of benzphetamine and d-amphetamine were compared. This is the study of Poindexter[4] who actually carried out a four-way double blind study comparing benzphetamine, phenmetrazine, d-amphetamine and placebos. He found that benzphetamine was superior to d-amphetamine in terms of weight loss, which was statistically significant. Since Poindexter's methodology was so much more complex and in many respects different than the procedure employed by us in this study, it was impossible directly to compare his findings with ours other than to note his conclusion.

The incidence and nature of side effects reported for the two drugs tested in this study were about the same. It was of interest to compare this with the side effects previously reported by us of a group of patients receiving placebos consisting of the same number of patients and of very similar composition in terms of age and weight. In a group of twenty such patients, five complained of nervousness, two, respectively, of palpitations, dizziness, dryness of the mouth and nausea, and three, respectively, of malaise and poor sleep. However, twelve of these patients complained of poor appetite control by the placebo drug. It would appear that the side effects of the patients receiving placebo are roughly comparable to those reported by the patients receiving benzphetamine and d-amphetamine in this study. There are two alternative explanations for these findings: (1) either benzphetamine and d-amphetamine did not give some patients a

better sense of well-being than did the placebo tablets, although they lost more weight and did not complain as much about hunger; or (2) many of the so-called side effects of anorexic agents are in reality symptoms of obese patients trying to stay on a low calorie diet. In this last respect, the side effects reported in this study bear a striking resemblance to those reported by Keys et al.[8] in their classic controlled studies on human semi-starvation, which they have termed "semi-starvation neurosis." However, it should be emphasized that a definitive evaluation of subjective complaints such as reported here as side effects would require a more elaborate methodologic approach than was employed in this study. In this connection, it should be mentioned that in other studies by Schapiro and Bográn,[3] Stough,[5] Oster and Medlar[2] and Reiser et al.,[9] it was found that side effects in patients treated with benzphetamine (particularly those of central nervous system stimulation) could be minimized by either tailoring the dose of the drug to the individual patient or by using smaller daily doses. Satisfactory weight loss without stimulation could be achieved in many patients with daily doses of benzphetamine of less than 100 mg.

Finally, if both drugs tested in this study, benzphetamine and d-amphetamine, were found to be equipotent in anorexigenic activity, and not significantly different in side effects, is there any clinical advantage in introducing another amphetamine drug for the treatment of obesity? The answer is yes. This positive assertion is based upon careful observation of the response of obese private patients to various amphetamine drugs over a period of several years. No one amphetamine drug is effective in *all* patients. No one drug is free of disturbing side effects in *all* patients. No single available amphetamine compound universally produces a significant anorexic effect with an accompanying sense of well-being in all patients. Some patients respond best to one drug, some to another. The amphetamine drug of choice must be tailored to the individual patient. In view of these practical observations of the *individual* obese patient, it is our conclusion that the more effective anorexigenic agents available, the larger and more potent is the therapeutic armamentarium available to the supervising physician.

SUMMARY

A double blind study was performed comparing the efficacy of benzphetamine (Didrex) and d-amphetamine in the management of obese outpatients. It was found that both drugs were equally effective in inducing weight loss, which averaged 1 pound per week over a fifteen- to sixteen-week period for patients treated by each drug. It was found that 40 to 80 mg. benzphetamine was equivalent in anorexigenic potency to 5 to 10 mg. of d-amphetamine. Side effects registered for patients in both drug groups were similar in nature and frequency. Comparison with side effects noted in patients receiving placebos in previous studies suggested that some of the side effects were in reality the symptoms of obese patients undergoing semi-starvation on low calorie diets, rather than true effects of the drugs in question. In this and other studies, benzphetamine has been demonstrated to possess significant anorexigenic activity, and therefore is a useful aid in the management of obesity.

REFERENCES

1. Simkin, B. and Wallace, L. A controlled clinical trial of benzphetamine (Didrex®) in the management of obesity. *Current Therap. Res.*, 2: 33, 1960.
2. Oster, H. and Medlar, R. A clinical pharmacologic study of benzphetamine (Didrex®). A new appetite suppressant. *Arizona Med.*, 17: 398, 1960.
3. Schapiro, M. M. and Bográn, N. Dietless weight loss with benzphetamine (Didrex®). A controlled comparison with phenmetrazine and placebo. *Current Therap. Res.*, 2: 333, 1960.
4. Poindexter, A. Appetite suppressant drugs. A controlled clinical comparison of benzphetamine (Didrex®), phenmetrazine, d-amphetamine and placebo. *Current Therap. Res.*, 2: 354, 1960.
5. Stough, A. R. Efficacy, persistence, and tolerance studies of the appetite suppressant, benzphetamine hydrochloride (Didrex®), with observations on patients given the drug as long as 30 weeks. *J. Oklahoma M. A.*, 53: 760, 1960.
6. Jolliffe, N. and Alpert, E. The "performance

index" as a method of estimating effectiveness of reducing regimens. *Postgraduate Med.*, 9: 106, 1951.

7. SIMKIN, B. and WALLACE, L. Some quantitative observations on a methamphetamine-phenobarbital anorexic compound in obese outpatients. *Am. J. M. S.*, 239: 533, 1960.
8. KEYS, A., BROZEK, J., HENSCHEL, A., MICKELSEN, O. and TAYLOR, H. L. The Biology of Human Starvation. Minneapolis, 1950, The University of Minnesota Press.
9. REISER, P., CHERICO, P., PALM, A., WAINER, D., PRINTZ, P. and HARRIS, S. B. The use of the appetite suppressant, benzphetamine (Didrex®), in general office practice. *Internat. Rec. Med.*, 174: 94, 1961.

Diet Therapy

Nutrition Services in State Departments of Health

Retrospect and Prospect

ANNA DE PLANTER BOWES, B.S., M.A., F.A.P.H.A.*

RESTROSPECT—EARLY SERVICES

THE Massachusetts Department of Public Health was one of the first to realize the value of nutrition in a public health program. In October 1917 a nutritionist was appointed to its staff of Child Hygiene. Her duties, as suggested by her title, Health Instructor in Food, were educational in character. Nutrition services in this state have been maintained continuously to the present time.

Gradually other states added nutritionists to their staff. However, until the passage of the Social Security Act in 1935, only a few states had budgetary provision for nutrition services. Financial assistance from the Children's Bureau to states and territories has been a definite factor in establishing nutritionists as members of the health team. High maternal and infant morbidity and mortality rates, severe malnutrition among preschool and school-age children were early and major concerns of the Children's Bureau. Recognition of the close relationships of a poor or inadequate diet to these conditions among mothers and children made the appointment of nutritionists in health departments a logical step in efforts to improve maternal and child health.

Nutrition classes for expectant mothers, food demonstrations and consultations in child health centers and "well baby clinics," cooking lessons for the foreign-born and nutrition classes for underweight children in schools were important areas of service in the nineteen-twenties. Vitamins, newly discovered, needed explanation and interpretation in family meals. These were considered needs at the local and state levels.

The depression of the nineteen-thirties focussed special attention on protecting family health at minimum or low cost. Getting the most for the food money was needed information for many families and individuals. Using low cost foods was a new experience for many families including highly skilled professional workers who had lived "very differently" before unemployment. Emergency child and family feeding programs, protecting the health of older youths through the National Youth Administration (NYA) and the civilian camp organizations (CCC) brought many added requests for service to nutritionists in state and local departments of health and welfare.

Planning budgets for an emergency, at low cost, or for rehabilitation of individuals or families who were malnourished or ill became a major service of the nutritionist. This brought her into increasing contacts with social and welfare agencies. Together, social workers,

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home economists in the social agencies and nutritionists developed the "relief standards" for use in the community and state.

This relationship has had many outgrowths that have deepened the understanding of all the professional workers concerned. Nutritionists became much more aware of the impact of social and emotional conditions on health and nutritional status of individuals and families. No college courses in the home economics curriculum or at the graduate nutrition level can give the same insight in understanding social forces on human beings that direct contacts with social workers and the families they serve can give.

A keener realization of the importance of nutrition for health and well being also influenced the thinking of social workers and even the curriculum of many schools of social work. Courses in nutrition have increased or have been added as the role of nutrition for total well being and human behavior has become better understood and appreciated.

SOME PIONEERS IN PUBLIC HEALTH NUTRITION

The growth and development of nutrition services in health departments owe a genuine debt of gratitude to the early pioneers of the field of nutrition education. Their labors, studies, reports and willingness to give field training directly, or in cooperation with universities and colleges, have provided many nutritionists with the information and skills now being translated into health department programs in all parts of this country.

Large urban centers such as Boston, New York, Philadelphia, Chicago and Cleveland had specific health and nutrition problems in direct proportion to population, unemployment, racial and health problems and the number of foreign-born families struggling with their new environment.

The Boston Dispensary and the name of Frances Stern will always evoke cherished memories in the minds and hearts of thousands of families in the New England and Boston area. Her basic knowledge of nutrition, coupled with unlimited vision of the cultural and social implications of food, and her rare devotion to promoting nutrition education for the humblest immigrant and the most brilliant professional visitor alike, have given much fruitful meaning to the promotion of food clinics and other forms of nutrition programs in all parts of the world.

In the New York City area, the name of Lucy H. Gillett is equally revered. During her long years as Superintendent of the Nutrition Bureau for the Association for the Improvement of Condition of the Poor (A.I.-C.P.) (now the Community Service Society) she and her staff interpreted good nutrition for health to thousands of families and hundreds of students privileged to secure field training from her. One of her many outstanding and enduring achievements is the report prepared as Chairman of the Subcommittee on Nutrition for Nutrition Services in the Field for the 1930 White House Conference on Child Health and Protection.[1] This report summarizes types of nutrition services in some state and local agencies through the year of 1930. Another publication by Miss Gillett, *Nutrition in Public Health*,[2] released in 1946, has been on best-seller lists for many years. It is well known to present day nutritionists and is often referred to as their public health nutrition Bible.

In Philadelphia, Emma Smedley gave the now thriving national school lunch program its firm beginning. Her book, *Institution Recipes*, and her skills at organization helped many school lunch managers begin their careers in providing appetizing and nutritious foods for millions of school children.

Inspiring teachers such as Mary Swartz Rose, Henry C. Sherman, Lydia J. Roberts and Elmer V. McCollum, at many universities and colleges, through their personality, research and writings have provided background for successful programs now in operation from Puerto Rico to Alaska and Hawaii and every other state in the Union.

To these few pioneers mentioned, many other names could be added. In each state, devoted research workers, physicians, dietitians and nutritionists have valiantly year by year inspired their pupils with the zeal and the scientific tools to become efficient workers in public health nutrition. The candles they

have lighted are throwing long beams on present day state nutrition programs.

CURRENT PROGRAMS IN STATE HEALTH DEPARTMENTS

The over-all goal of nutrition services is the improvement of nutritional status of all the people at all age levels and in all socioeconomic groups. Additional goals are:

To provide guidance in nutrition for optimum *growth* and *development* of children, for maintenance of health in adults at high levels and for the prevention of disease and early onset of certain debilitating diseases of the later years.

To assist in rehabilitation. Nutrition can play a vital role in rehabilitation of children with orthopedic disabilities, with rheumatic heart disease, with cleft palate, and of people of all ages with tuberculosis, diabetes, cardiovascular disorders, hepatitis and many other diseases.

How these goals will be spelled out into programs of action will vary from state to state, city to city, and from one local community to another. *Nutrition needs of the people at the time* should be a first and major basis for developing programs.

HOW CAN NUTRITION NEEDS BE DETERMINED?

Food habit surveys and dietary inventories of expectant mothers, children, adults in various professional and occupational classifications, and of the aged will provide information on food practices. The findings of medical and dental examinations of various population groups, and the morbidity and mortality rates at state and local levels will provide much background information. Well planned food consumption surveys and nutritional status studies of various groups, correlated with medical findings, give the most detailed data.

How many of these activities can be carried out will depend on the number of nutritionists and nurses on the staff of the state health department and at the regional, county, city or local levels. Liaison in research projects with medical schools, schools of public health and home economics, with federal agencies and private foundations will also determine how much nutrition research can be conducted on a cooperative basis. Long-term or short-term research projects in many states have greatly strengthened nutrition programs and convictions about the close relationship of nutrition to health.

Translating the findings of activities which will point up nutrition needs into a plan of action for the most efficient use of the nutritionist's background and skill requires joint effort on the part of many individuals and many agencies.

The physician responsible for administering the total health program in a state[3] is in a key position to determine the integration of nutrition into the various units of his department and in community agencies. The frontiers of public health he surveys have expanded greatly in the past decade. To the physician-nurse–nutritionist–social worker team of the earlier decades, new forces have been added. In each state an increased number of specialists in the medical, nursing, social and behavioral sciences now comprises the health team. In planning a state nutrition program each of these must be considered.

FITTING NUTRITION NEEDS INTO THE TOTAL HEALTH PROGRAM

Some Present Day Areas for Nutrition Education

Good nutrition has its greatest potential in contributing to future health during the preconceptional and prenatal periods.[4–6] Nutrition education efforts should be directed to expectant mothers, young women and adolescent girls. The trend toward earlier marriages and the recognized poor nutritional status and food habits of many teen-agers accentuate the importance of services to these critical groups.

Psychologists, food technology and the supermarket have increased the decisions mothers of infants and preschool age children must make about *what* to give their children and *how* to develop good food habits. Nutrition guidance has become *more* rather than *less* intricate and involved than in the nineteen twenties or thirties.[7–9]

Schools, at elementary and higher levels, need to continue nutrition education. School

buses rather than the former walks to school, the increased tempo of living at home, at school, and after school, consolidation and urbanization of schools and population, the school lunch system, television and movies have specific impact on eating patterns and food and nutrition. No or poor breakfasts, undesirable snacks and irregular meals at home have direct relationship to the poor nutritional status of many school children, especially those of teen-age.[10]

The nutrition of adults is subjected to many present day hazards: poorly planned and scheduled meals due to travel and occupational irregularities and hazards, reduced physical exercise, increased emotional and physical stress and tensions due to overcrowding and many other factors.[11]

Alcoholism, narcotic addiction and the early onset of chronic and/or debilitating diseases present other nutritional considerations.

Obesity at all age levels presents its special hazards to good nutrition and health. Its association with diabetes, cardiovascular, arthritis and other chronic illnesses makes the effort directed toward group and individual instruction a nutritional responsibility.

Year by year, the number of older people in our states increases. This has created many health problems in homes, in institutions and for the community or state. Chronic diseases are most prevalent in this group of our population. Most chronic diseases require many dietary adjustments or changes.[12]

Many convalescent and nursing homes for the aged do not employ well trained personnel for food service. Poorly planned meals, unsavory and unappetizing in appearance and/or service are all too common. Nutrition consultant service and an in-service educational program through conferences, workshops and institutes are needed.

In institutions for children, at summer camps and for migrant labor, nutrition can also be improved by consultation or other forms of education.

Unemployment, strikes, relocation of industrial corporations, accidents and illness usually create severe financial problems or crises in families. Guidance in adjusting family meals to lowered income and the use of surplus foods is needed by the nurses and social workers in contact with these families.

These are some areas of nutrition to which program efforts are directed in many states. Specific health conditions, epidemics, racial or nationality group health needs will receive priority in other states.

WAYS TO MAKE PROGRAMS FUNCTION

Provide practical nutrition information for professional colleagues and lay groups at various age and socioeconomic levels. Nutrition is a dynamic and changing science. Research and food technology adds to, changes or modifies current information on food and its use.

The nutritionists or nutrition staff must continuously analyze these changing facts and interpret them in simple language. Leaflets, pamphlets, food manuals, food value charts, exhibits, radio and television releases and magazine articles to meet specific requests can reach large groups. Food demonstrations and verbal presentations at clinics, meetings of all types and conferences are also effective.

Give consultant service upon request to all units in official state agencies, local agencies, local school districts, voluntary agencies and industries.

This is the most efficient use of the nutritionist's services in most states. Through participation in staff conferences, nutrition information can be shared with other members of the health team who have broad contacts with groups and individuals. Assistance on special programs or projects often includes (1) preparation of family food budgets and special diets for use by nurses and social workers; (2) technical guidance and cooperation on a demonstration basis in classes or discussions for groups of expectant parents, mothers of young children, overweight individuals, persons with diabetes, tuberculosis, cardiovascular disease, and individuals with special handicaps such as orthopedic conditions, cerebral palsy and mental retardation;[13] (3) assistance in planning many special projects in schools[14] such as animal feeding studies, "better breakfast," or school-lunch programs

and weight control classes; (4) integration of nutrition and dietary considerations in programs conducted by sanitarians, individuals in charge of accident prevention, and at treatment centers for alcoholics and other addictive diseases.

Offer in-service training for professional personnel: Workshops, institutes or technical conferences on nutrition may be initiated by the Nutrition Unit, by an official or nonofficial agency or by a college or university. The Nutrition Unit or consultant will act in an advisory capacity and supply members of its staff as consultants and speakers after clearance through proper channels.

Promote and cooperate in the development of nutrition activities in county and local health departments.

Stimulate the development of nutrition projects through cooperation with professional associations such as the state Medical Society, American and state Public Health, Dietetic and Home Economics associations.

Give direct services in nutrition when they can be arranged on a demonstration basis, as in-service training for professional personnel in an agency.

Cooperate with other departments such as Public Instruction and Public Welfare in projects, conferences or workshops for promoting nutritional well-being of persons of all ages served by these agencies.

These are some ways of integrating nutrition services into the total health program. Various other activities are in progress in many states.

A LOOK AHEAD

Current nutrition research at universities and colleges, at medical centers and institutes of health in this country and in similar institutions around the world provides increasing evidence of the close relationships of nutrition to health at all ages—mental, social and physical.

At the White House Conference on Children and Youth in 1960, nutrition may well be an even greater consideration than in 1930 in preparing today's youth for living in tomorrow's world.

And from the 1961 White House Conference on Aging it is safe to predict that research will contribute in many unforeseen ways to help men and women enjoy their golden years in better nutritional status.

REFERENCES

1. Nutrition Services in the Field. White House Conference on Child Health and Protection. New York, 1932. The Century Co.
2. Gillett, L. H. Nutrition in Public Health. Philadelphia, 1946. W. B. Saunders Co.
3. Nutrition Practices: A Guide for Public Health Administrators, 1955. The American Public Health Association.
4. Stearns, G. Nutritional state of the mother prior to conception. Council on Foods and Nutrition, *J.A.M.A.*, 168: 1655, 1958.
5. Hepner, R. Maternal nutrition and the fetus. Council on Foods and Nutrition, *J.A.M.A.*, 168: 1775, 1958.
6. Gentry, J. T., Parkhurst, E. and Bulin, G. V., Jr. An epidemiological study of congenital malformations in New York State. *Am. J. Pub. Health*, 49: 597, 1959.
7. Proceedings of The Borden Centennial Symposium on Nutrition. New York, 1958. The Borden Company Foundation, Inc.
8. Vitamin Preparations as dietary supplements and as therapeutic agents. Council on Foods and Nutrition, *J.A.M.A.*, 169: 41, 1959.
9. Kraybill, H. F. Nutritional and biochemical aspects of foods preserved by ionizing radiation. *J. Home Economics*, 50: 695, 1958.
10. Mack, P. B. and Bowes, A. Nutrition of Older Boys and Girls. Denton, Texas, 1955. Texas Woman's University.
11. Rosen, G. and Wellin, E. A bookshelf on the social sciences and public health. *Am. J. Pub. Health*, 49: 441, 1959.
12. Katz, L., Stamler, J. and Pick, R. Nutrition and Atherosclerosis. Philadelphia, 1958. Lea & Febiger.
13. Bricker, A. J., Judson, J. S. and May, E. Planning for rehabilitation service. *J. Home Economics*, 50: 701, 1958.
14. Jacobson, W. J., Boyd, F. L. and Hill, M. Promising Practices in Nutrition Education in the Elementary School. New York, 1959. Teachers College of Columbia University.

Letter to the Editor

Coronary Heart Disease in South African "Poor Whites" and White Prisoners Habituated to a Bantu Type of Diet

Dear Sir:

Electrocardiographic and other relevant investigations are being undertaken on groups of nonhospitalized Bantu (primitive and sophisticated), Asiatics, "poor whites," and middle class South African whites. The The electrocardiographic studies thus far undertaken on the Bantu (1,800 subjects) point to a very low incidence of myocardial infarction, a finding in agreement with the reported rarity of the condition found at necropsy.[1–3] The observation which we wish to discuss here is the apparently low incidence of infarction in indigent whites (poor whites), as detected by electrocardiographic studies undertaken and interpreted as described in the recent WHO publication on "Hypertension and Coronary Heart Disease."[4]

Up to the present, 340 subjects (201 men, 139 women) have been examined; 233 (141 men, ninety-two women) ranged in age from forty to seventy-eight years, the average age being fifty-three years. Two men,* aged sixty-five and sixty-seven years, respectively, gave evidence of infarction, indicating an incidence of 1.5 per cent in the older male group and zero incidence in the older female group. Furthermore, no subject gave unequivocally positive replies to the three leading questions which were used in the Los Angeles cardiovascular study, and designed to elicit evidence of angina pectoris.[5]

In comparison, in a study on Indians at New Delhi,[6] electrocardiographic studies revealed no case of infarction in sixty-two poor workers aged eighteen to seventy years, and two cases (2 per cent) among 100 business and professional men aged twenty to sixty-five years. In the Los Angeles investigation[5] combined electrocardiographic evidence and replies to questions indicated "coronary arteriosclerosis" to be present in forty-seven of 1,125 men (4.2 per cent) aged forty through sixty plus years. Regarding other somewhat comparable studies, Weitzman and Smith[7] investigated 100 hospital patients aged fifty to eighty years with no clinical evidence of cardiac disease; myocardial ischaemic tracings were noted in ten subjects (10 per cent), the number increasing to twelve (12 per cent) after exercise; six of these patients subsequently died and gave evidence of ischaemia at postmortem examination. Wosika et al.[8] (on the basis of electrocardiographic studies) reported the condition present in 21 per cent of clinical healthy subjects over eighty years. In our own studies, obviously, far more observations will need to be made on "poor whites" before we are able to define their apparently advantageous position regarding myocardial infarction and angina pectoris. Unfortunately, such studies are protracted being undertaken on house-to-house, or more often farm-to-farm visits. At this juncture the only tentative inference which we wish to make, and are bringing forward because of its ramifications, is the apparently low prevalence of coronary heart disease in a white population, not underweight, and habituated to a Bantu pattern of diet, i.e., very high carbohydrate (maize and wheaten bread, 1 to $1^1/_2$ pounds dry cereal per diem), and very low in

* The presence of myocardial infarction in the first "poor white" subject, aged sixty-five years, is not completely certain.

animal protein and fat (especially animal fat). This relatively low incidence of the disease in poor people, qualitatively, is not unexpected bearing in mind that in England it has been shown that mortality from coronary heart disease in social class I is double that in social class IV.[9]

The second point concerns South African white prisoners who consume a diet very high in crude fibre and carbohydrate (over 1 pound dry cereal per diem) and low in fat, although not low in calories or in protein (animal and vegetable). Among long-term prisoners, death from coronary heart disease during detention is believed to be very rare. Thus, in Pretoria Jail, which accommodates about 600 white prisoners, in the past thirty-two years in only one man of thirty-seven men who died during confinement was death certified as being due probably to coronary thrombosis, and this person was a newcomer. Prisoners, of course, are a very selected population; in addition they are probably more active and smoke less than those at liberty; moreover, while certainly not free from stress, they do not experience the "deadline date" type of life,[10] nor the competition associated with nonprison conditions. In our view, however, the change of greatest magnitude that takes place among them is that of diet. Here again, qualitatively, this finding is not unexpected. The war-time experience of Norway and Finland, despite certain anomalies that have been pointed out,[11] leaves little doubt that at the period when the national diet became higher in carbohydrate and lower in fat, there was a reduction in mortality from coronary heart disease.[12]

Assuming that further work confirms that "poor whites" do indeed have a low incidence of coronary heart disease, and that white South African long-term prisoners seldom die from the disease, it would seem permissible to make two comments: (1) It should now be possible to fully characterise a white population among whom coronary heart disease presents no public health problem. (2) Among the white prisoners, not necessarily years, but apparently only months of the type of context described would seem to be sufficient to greatly reduce or even prevent deaths from coronary heart disease. It is important to stress that such protection obtains in the presence of ample calories and protein (animal and vegetable). Despite this highly practical point, it is imperative to emphasize that insofar as diet is responsible, to reach this favorable outcome the requisite degree of departure from an average white diet is very considerable.

The foregoing comments are made entirely on the assumption that further work confirms the items of evidence cited on the "poor whites" and white prisoners. Additional work on the former, while time-consuming, is straightforward. If confirmatory, the next stage of endeavour will be to determine and characterise the highest economic stratum of the South African white population between "poor whites" and the more favored class of whites,* which has a low incidence of coronary heart disease. The situation regarding the apparent rarity of acute coronary episodes in white prisoners lends itself to relatively early confirmation or otherwise by means of clinical and electrocardiographic studies conducted along two avenues of approach: (1) Establish the incidence of coronary heart disease in newcomers; then determine the incidence in groups who have served five and ten year sentences; the incidence in the long-term prisoners should be that of their age periods at the time of commencement of detention, and not that of their chronologic ages. (2) Determine the incidence of infarction in newcomers, and then again after perhaps two- and four-year intervals; there should be no increase in incidence of the condition comparable to that found in nonprison white populations. For example, in the Los Angeles study,[13] among men with "normal hearts" at the beginning of observation periods, the annual increase in incidence was 0.8 per cent at forty to fifty-four years, and 2.9 per cent at fifty-five to seventy years. If our investigations are successful, it should be possible to define the diet and manner of life which even when adopted for relatively short

* Subsequent studies on additional "poor white" groups suggest that a relatively low incidence of coronary heart disease prevails only in the lower economic stratum of such populations.

periods, is associated with a low mortality from coronary heart disease.

The carrying out of the research work described is being supported in part by a grant (H: 4244) from the American National Heart Institute, U. S. Public Health Service Bethesda, Maryland.

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REFERENCES

1. BECKER, B. J. P. Cardiovascular disease in the Bantu and Coloured races of South Africa. v. Hypertensive heart disease. *South African J. M. Sc.*, 11: 107, 1946.
2. HIGGINSON, J. and PEPLER, W. J. Fat intake, serum cholesterol concentration, and atherosclerosis in the South African Bantu. II. Atherosclerosis and coronary artery disease. *J. Clin. Invest.*, 33: 1366, 1954.
3. SCHRIRE, V. and UYS, C. J. Cardiac infarction in the Bantu. *Am. J. Cardiol.*, 2: 453, 1958.
4. First report of the Expert Committee on Cardiovascular Diseases and Hypertension. Hypertension and coronary heart disease. *Bull. World Health Organ Techn., Rep. Ser.*, no. 168, 1959.
5. PHILLIPS, E., CHAPMAN, J. M. and GOERKE, L. S. Relative values of techniques used in detection of heart disease. *Am. Heart J.*, 43: 319, 1953.
6. PADMAVATI, S., GUPTA, S. and PANTULU, G. V. A. Dietary fat, serum cholesterol levels and incidence of atherosclerosis and hypertension in Delhi. *Circulation*, 19: 849, 1959.
7. WEITZMAN, D. and SMITH, E. B. Ischaemic electrocardiograms in symptomless men with a note on the serum lipoproteins. *Brit. M. J.*, 2: 162, 1959.
8. WOSIKA, P. H., FELDMAN, E., CHESROW, E. J. and MYERS, G. B. Unipolar precordial and limb lead electrocardiograms in the aged. *Geriatrics*, 5: 131, 1950.
9. MORRIS, J. N. Incidence of coronary disease in population groups in England. In: Cardiovascular Epidemiology. World Trends in Cardiology, vol. 1, p. 42. Edited by Keys, A. and White, P. D., New York, 1956. Paul B. Hoeber.
10. ROSENMAN, R. H. and FRIEDMAN, M. The possible relationships of the emotions to clinical coronary heart disease. In: Hormones and Atherosclerosis, p. 283. Edited by Pincus, G. New York, 1959. Academic Press.
11. MORRIS, J. N. Epidemiology and coronary heart disease. *Circulation*, 17: 321, 1958.
12. BIORCK, G. Wartime lessons on arteriosclerotic heart disease from Northern Europe. In: Cardiovascular Epidemiology, World Trends in Cardiology, vol. 1, p. 8. Edited by Keys, A., and White, P. D. New York, 1956. Paul B. Hoeber.
13. CHAPMAN, J. M., GOERKE, L. S., DIXON, W., LOVELAND, D. B. and PHILLIPS, E. Measuring the risk of coronary heart disease in adult population groups. The clinical status of a population group in Los Angeles under observation for two or three years. *Am. J. Pub. Health* (suppl.) 47: 33. 1957.

ASCN News

The Formation and Goals of The American Society for Clinical Nutrition

Presidential Address—April 29, 1961

RICHARD W. VILTER, M.D.

IN AUGUST 1959, I received a letter from Dr. Robert Goodhart outlining some correspondence with Dr. Robert Olson and Dr. Omi Waife relative to a clinical nutrition society. At first I mistook their meaning, and visualized a new American Board of Clinical Nutrition in the making. I am sure you know how strongly I oppose the formation of any new subspecialty boards, since some of the existing ones, in essence, are fragmenting medicine and surgery, and through economic leverage are attempting to dictate postgraduate education policies to the universities. So I concocted a sizzler in reply, but fortunately, before I mailed it, I reread the correspondence. I found to my chagrin that my friends wanted opinions from many nutritionists on the appropriateness of founding a clinical nutrition society to promote better educational efforts and more research in the field of human nutrition. This, of course, was an entirely different matter.

My answer, and apparently many others, was in the affirmative with several provisos: That the purpose of a new society be the improvement in graduate and undergraduate training in clinical nutrition, the promotion of good research in these areas, and that it meet in conjunction with a clinical society of the stature of the American Society of Clinical Investigation to keep at a minimum the number of trips which, of necessity, all of us must take.

On September 2, 1959, an initial meeting was held at the Hotel Carlyle in New York to discuss the formation of a society for clinical nutrition. There was agreement that the idea of creating a society for clinical nutrition was a good one, that Drs. Robert Goodhart, Robert Olson and Theodore van Itallie should determine and define the purposes and standards of the society, and that a group of physicians should constitute the charter members of the society.

Prior to a preorganization meeting in New Orleans in October 1959, much important ground work was done by Dr. Goodhart and his associates in New York. Just before the New Orleans meeting, The American Society for Clinical Nutrition was incorporated in the State of New York with Drs. Robert Goodhart, Theodore van Itallie, Norman Jolliffe, Maurice Shils and Michael Wohl as directors. Under the able chairmanship of Dr. Grace Goldsmith, a temporary organization was set up and acting committees were appointed.

It was evident even before this meeting that The American Institute of Nutrition, of which many of the founding group were members, was of the opinion that a disservice would be done to the promotion of good nutrition in the United States if there were two competing groups—the one oriented toward clinical medicine and the other interested primarily in the basic sciences. After a great deal of negotiation and collective bargaining, a formula agreeable to both groups was reached whereby the embryonic clinical society would become a semiautonomous section of the Institute with the right to hold its own meetings, operate its own journal and determine its own membership requirements.

Having established the basis for a united front, Dr. Goodhart held a meeting of the Executive Committee in Chicago in April

1960 to plan for the final organization meeting which was held in Atlantic City on May 1, 1960. At the latter meeting, attended by Dr. Woolley for The American Institute of Nutrition, and by about forty physicians interested in the new society, a general outline of a constitution was worked out, section by section. The acting committees were dissolved and officers, the present incumbents, were elected.

You have already heard the reports on the major accomplishments during the past year. A very salutary agreement has been reached with the Reuben H. Donnelley Corporation, through the good offices of Mr. Pliny Porter, by which *The American Journal of Clinical Nutrition* has become the official organ of our Society and the treasury has been bolstered by a dependable source of income. Relationships with The American Institute of Nutrition have been solidified, the constitution has been revised and accepted by Council, the membership has been increased through the efforts of Dr. Robert Kark and his membership committee, and this meeting with the excellent program that awaits you has been planned.

I cannot forego this opportunity to pay high tribute to our secretary, Dr. Robert Hodges, who has done the lion's share of the work which made this Society a going concern. I wish to pay tribute also to Dr. Robert Goodhart, who has guided the embryonic development of the Society and served as its accoucheur. The Council, Drs. Robert Olson, William B. Bean, Willard Krehl and Robert Goodhart, has been most energetic and helpful.

And so, a new society has been born to encourage undergraduate and graduate education in human nutrition in health and disease, to provide an opportunity for investigators to present and discuss their research findings in human nutrition, to provide a journal for the publication of meritorious work on experimental nutrition, and to unify the science and practice of nutrition as it relates to clinical medicine.

It is my opinion that the first of these objectives for which the society must work is the improvement of nutrition education in medical schools. Recent surveys indicate how woefully inadequate it is. Most schools pay lip service to nutrition education but do little else. In part, this is a revolt against the misconception of our forefathers who prescribed diets of doubtful value because they had little knowledge and nothing else to prescribe. It is a revolt against quacks and food faddists who have given the science of nutrition a bad name. It is due to dissatisfaction with the concept that nutrition is synonymous with dietetics or with the agricultural sciences when, in fact, it is the expansion and application of that great mass of basic knowledge that we call biochemistry for the improvement of mankind's health. Dietetics provide the mechanism of translating that knowledge into actual food consumed. The basic and agricultural sciences often point the way to new discoveries, but it remains for the physician, and the scientists associated with him, to demonstrate the importance of food factors to the maintenance of good health and the elimination of disease in man.

Every medical subject, from the first year of medical school through all the postgraduate years, contains elements of great importance to good health through proper nutrition. Biochemistry forms the cornerstone of the field. A large segment of the course in preventive medicine and public health should deal with nutrition, for the object of the nutritionist is to prevent disease so that his patient will be spared the physical suffering and economic loss attendant upon curing it. Recognition of the physical signs of deficiency disease should be a part of every course in physical diagnosis; nutrition looms large in pre- and postoperative surgical care, in the treatment of burns and physical trauma, and in the healing of wounds. In psychiatry, one has the problems of anorexia and overeating; in obstetrics, the impact of nutrition on the health of the mother and the vitality of the infant; but the greatest burden of instruction in clinical nutrition, both at the undergraduate and postgraduate levels, lies in the fields of internal medicine and pediatrics.

In some schools, these areas are covered quite thoroughly, but in most they are scarcely mentioned. In schools in which there is much interest in nutrition among faculty members, there may be a lecture course in nutrition,

usually in the third medical school year. However, there is an increasing tendency to reduce the number of lectures with which medical students are bombarded, and to emphasize conferences, small group discussions and careful study of patients at the bedside or in the clinic where specific and pressing problems of patient care leave an indelible mark on the mind of the receptive, inquiring student. Lectures are valuable, and always will be, for painting the broad picture of a subject for the student, for giving him perspective and for pointing the way to further reading and study. It will be impossible, however, to accommodate with lecture series all the new fields, such as biophysics, genetics and immunology, which are impinging on medicine now. It also seems unlikely that free time for nutrition lectures will be found in most medical school curricula.

Correlative teaching is becoming more and more fashionable because it conserves time, eliminates duplication and provides better organization of subjects for the student. In some schools a committee with members from various departments is given the responsibility for all basic instruction concerning a particular organ or system. In the light of these developments, I believe that each school should have a coordinator of education in nutrition. To be effective, he must be a good clinical investigator and should have an active, interesting research program under way. He must have a solid background in biochemistry, and he must also be an accomplished internist, pediatrician or surgeon, depending upon the clinical department to which he owes allegiance. He must be able to attract bright young men to work with him, men who can help with the coordination plan. It must be his job to ferret out all the places in the curriculum where nutrition education will have a beneficial impact, and to make sure that the subject is covered adequately. He and his group should be responsible for any survey lecture time that may be allotted, and with his team he must bring the principles of good nutrition to the bedside.

This is the goal expressed in our constitution. It is the work to which we must dedicate ourselves in the years ahead. Good nutrition education will foster research, and research will act as a catalyst for even better education. It is a goal that can be achieved, but we must have vigorous and enthusiastic members on the faculty of every medical school in the United States and Canada, and the activities of these members must be stimulated by a committee of this society.

Reviews of Recent Books

Recent Advances in Human Nutrition, by J. F. Brock, Little, Brown & Co., Boston, 454 pp., $11.50.

In my opinion, this is one of the most important books on clinical nutrition in recent years. There has long been an acute need for a critical summary of the rapidly advancing development in human metabolism and nutrition, not only to collect in one convenient place the data being obtained all over the world, but also to summarize and place them in proper perspective. This is done by Professor Brock and his fourteen experienced contributors.

The editor himself has written about half the book. Others, including György, Holt and Scrimshaw from this country, cover certain specialized topics. Of special interest is the editor's chapter on "Some General Trends and the Future" with its discussion of the population explosion and nutrition education in medical schools and hospitals. Our readers will also be interested in Jackson's comment that "There appears to be no good evidence in favor of supplementing the calcium in the diet of any normal healthy person in any circumstances whatever. Habituation to a low calcium intake may even be of value to the organism."

Much new work is cited (some references are from 1960) and there is a brief summary of review papers presented at the Fifth International Congress on Nutrition (September 1960).

According to the authors, "constitution" is determined in part by the habitual diet and this must be considered in discussing the etiology of the degenerative diseases of middle life. "This may be the most important lesson coming from the study of clinical nutrition to influence thought in the 1960's." This is reflected in the multiple references to our nutritional standards, particularly as they relate to so-called underdeveloped areas. The obvious importance of these concepts makes them, and this book, indispensable to all who are interested in human nutrition, health and disease. A vote of thanks and a word of appreciative congratulations to the authors for undertaking the task and producing such excellent results. S.O.W.

Human Pituitary Hormones. Ciba Foundation Colloquia on Endocrinology, Vol. 13, edited by G. E. W. Wolstenholme and C. O'Connor. Little, Brown & Co., Boston, 1960, pp. 336, $9.50.

This book does an admirable job of bringing a major portion of the field relating to pituitary hormones up to date with particular reference to material obtained from human glands. Evaluation of fractionation technics indicates that those which have been successful for animal pituitaries do not give adequate separation and yield of specific fractions in human material. Growth hormone and the gonadotropins appear to have been separated in a reasonably adequate fashion. The use of immunologic technics for assay of growth hormone appears to have promise. A variety of metabolic effects of growth hormone are considered, including regulation of lipid metabolism, protein metabolism, carbohydrate metabolism, and mineral metabolism. All these areas appear to be affected in some measure. Significant differences are observed in the degree of response between different subjects. The relationship of urinary gonadotropin levels to remissions following oophorectomy in patients with cancer is considered, as well as the use of this procedure for other purposes. Human corticotrophin appears to have the same amino acid composition as ovine and bovine material but differs from porcine. Interesting considerations regarding blood levels of the thyroid-stimulating hormone are presented.

In general, the book is a very worthwhile addition to the library of anyone with more than a passing interest in endocrine and metabolic disease.

L. W. KINSELL

Annual Review of Medicine, Vol. 12, edited by David A. Rytand. Annual Reviews, Inc., Palo Alto, 1961, pp. 408, $7.00.

We have come to look forward to the "Annual Reviews" as one of the best sources of critically evaluated summaries of research progress. This 1961 volume is no exception. Although nutritional topics *per se* get rather little discussion, malabsorption and iron metabolism are competently evaluated. Oral hypoglycemic agents and endocrine tissue transplantation are two of the new topics covered. This reviewer has found his collection of the Reviews a most useful aid for a quick search of the literature. No doubt their success is the consequence of fulfilling a widespread need. We look forward to next year's book.

S.O.W.

The Encyclopedia of the Biological Sciences, by Peter Gray. Reinhold Publishing Corp., New York, New York, pp. 1083, $20.00.

As the book jacket of this one-volume encyclopedia says "If it falls between abiogenesis and zoogeography

you'll find it in the valuable new reference work." This book of over 1,000 pages consists of more than 800 articles written by experts from many corners of the world. With numerous illustrations (but relatively few references) it is a remarkable collection of data for anyone interested in any biologic science. Some biographic sketches are presented, but emphasis is given to taxonomic, developmental and ecologic aspects. Obviously all of biochemistry, biophysics and the applied biologic sciences, including medicine, could not be included. Indeed, the sum total of man's knowledge is beyond the limits of books—and perhaps beyond electronic computers. However, the able editor explains the scope of this enterprise in the introduction and one must agree that the objective was fully realized.

There is a general discussion of nutrition (Stare) and a brief description of fat-soluble vitamins (Hodges) and the water-soluble group (Aaronson). No doubt the fact that the Pangolins (anteaters) receive more space than phospholipids reflects not the relative importance of the subjects, but rather the objective of the encyclopedia. Many currently "hot" topics appear in its pages, including biologic warfare, space biology, enzymology and genetics. Selkurt's discussion of renal function, for example, includes the new countercurrent concept.

For whom is the book intended? Apparently the objective was "to provide the maximum amount of information for the greatest possible number of people." This ambitious goal includes biologic scientists as well as nonprofessionals who desire information beyond the accounts in general encyclopedias. Librarians, graduates, college and even high school students and their teachers will find this a true gold mine of biologic information.

S. O. W.

Inter-African Nutrition Conference, Third Session, Vol. II, Inter-African Conference of Nutrition, Angola, Portugal, 1956, pp. 889.

The appearance of the proceedings of this conference in 1956 attended by representatives of many, perhaps all, of the countries south of the Sahara emphasizes the tremendous political events in recent years. Some of the countries represented have disappeared with a greater number being formed, a number of the speakers are no longer associated with Africa and undoubtedly all have had their lives and work influenced markedly by events in recent years.

This is the second volume of the papers presented. Many are published in two languages, either French, Portuguese or English, and summaries are available in all three languages. This results in a volume of 877 pages, a discouragingly large number. As with most conferences the quality of papers varies from excellent to very poor. The range of topics covers practically all areas of nutrition and these can be indicated only in general terms. A number of papers deal with the "protein problem," including studies on the biologic value and amino acid composition of protein sources, feeding trials with infants and clinical studies of kwashiorkor. Nutrition and agriculture and the utilization of local resources, nutrition education and the role of nutrition in public health programs, biochemical findings in various areas and in association with different nutritional deficiencies and nutrition surveys are other topics covered by several speakers. Perhaps the primary value to U. S. readers will be to provide and insight into some of the major nutritional problems of Africa and to indicate the kind and caliber of work being performed although some of the papers represent solid scientific contributions.

The long delay in publication is extremely unfortunate. One suspects that much in this volume is history.

D. M. Hegsted

Books Received for Review

Books received for review by *The American Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for extensive review.

Recent Advances in Human Nutrition, by J. F. Brock. Little, Brown & Co., Boston, 1961, pp. 454, $11.50.

Foetal and Neonatal Physiology, British Medical Bulletin, Vol. 17, No. 2. The British Council, London, 1961, pp. 176, $3.25.

The Encyclopedia of Biological Sciences, edited by P. Gray. Reinhold Publishing Corp., New York, 1961, pp. 1083, $20.00.

Fish. The Great Potential Food Supply, by D. B. Finn. FAO, Rome, 1960 (Columbia University Press, American Agents), pp. 47, $0.50.

Essential Hypertension, An International Symposium, F. C. Reubi, Chairman, edited by K. D. Bock and P. T. Cottier. Springer-Verlag, 1960, pp. 392.

Toward the Conquest of Beriberi, by Robert R. Williams. Harvard University Press, 1961, pp. 338 $7.50.

Abstracts of Current Literature

CHARLES R. SHUMAN, M.D., EDITOR

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RECENT CONCEPTS IN OBESITY

The accumulation of body fat is the consequence of a caloric intake exceeding caloric expenditure. While it is easy to measure caloric intake the determination of caloric needs has not been precisely appraised for the daily activities of most persons. Newer types of instrumentation now available should permit the accumulation of much significant data in this area. With a complete knowledge of caloric requirements for all types of activity an appropriate rating can be made for daily caloric balance.

The Causes and Cure of Obesity. J. Yudkin. *Lancet*, 2: 1135, 1959.

This is an entertaining dissertation which most people connected with practical problems of nutrition could read with profit.

"There is no evidence that man is immune from the laws of thermodynamics. In every conceivable way it has been proved that the accumulation of excessive fat follows the intake of excessive calories." The causes of the excessive intake are examined, in particular those which affected the satiety center in the hypothalamus—Joliffe's "appestat," genetics, hormones, drugs, exercise and social and psychologic factors. The author has shown that glucose seems to act as a stimulant to appetite. It is argued that obesity is not usually due to a metabolic defect and that the person who can "eat as much as I like" without becoming fat is a fallacy.

The two most common factors in overeating are a low physical activity and a temptation to eat too much, particularly of sweet foods. The chief aims of treatment should be to increase activity and to give a diet which is satisfying but lower in calories. In practice this means restriction of carbohydrates. According to the author, methyl cellulose may be a useful adjunct to depress appetite while new dietary habits are acquired.

F. E. HYTTEN

Etiology of Severe Obesity: A Study of Five Cases. M. B. Fertman. *J. Am. Geriatrics Soc.*, 7: 38, 1959.

Brief histories and laboratory tests of endocrine function on five very obese women are presented in this paper. None showed any evidence of endocrine disease but one had a history of encaphalitis. The author uses these rather ordinary case reports as a point of departure for a discussion of the mechanisms by which obesity develops. The discussion is heavily loaded with information from various studies of experimental obesity in animals, but form an incomplete review of the subject.

G. HOLLIFIELD

The following series of papers describes experiences with various types of weight-reduction programs. These include the simple restriction of size of food portions, group instruction, hypnosis and combinations of anorexigenic agents.

Modern Management of Obesity—The "Social Diet." M. Plotz. *J.A.M.A.*, 170: 1513, 1959.

One hundred consecutive patients, obese by the usual standards, were studied. Eighty-two of these were considered to be obese because of overeating. In the majority, motivation and cooperation were easily established. There were additional cases in which obesity was said to be unassociated with overeating and were mostly complicated cases of endocrine or metabolic disease.

The "social diet" is based on a moderate reduction in the quantities of all foods. No more than one slice of bread at any one meal is to be eaten. "Portions of

everything are to be reduced by about one-quarter." According to the author, almost every determined patient will lose weight on this regimen.

Under the conditions of clinical management as described in the paper, five of the eighteen "non-overeating" patients had a satisfactory weight loss, and sixty-three of the eighty-two other patients also responded. Best results were in those in whom motivation was said to be strongest.

This clinical experience is interesting. Unfortunately, the personality of the physician and the circumstances of the therapeutic management are such that results cannot or need not necessarily be transposed to other situations. S. O. WAIFE

Stepwise Weight Reduction in Obese Young Women: Clinical and Metabolic Responses. C. M. Young, A. M. Brown, B. A. Gehring and B. M Morris. *J. Nutrition*, 70: 391, 1960.

A fair number of people can accept rigid caloric restriction over short intervals of time but not for prolonged periods. There would seem to be a psychological advantage in allowing "rest periods." This study was undertaken to determine whether there may be also a physiologic advantage.

It had been observed that over long periods of weight reduction human subjects begin to lose nitrogen, calcium and phosphorus. Then, when changed from a reducing to a maintenance diet, they reach a state of equilibrium or retention with regard to all three nutrients.

Ten overweight young women were used in this study, divided into two groups of five each. One group was subjected to stepwise weight reduction, the other was kept on maintenance diets. The feeding period was sixteen weeks. Determined at intervals were nitrogen, calcium and phosphorus balances, measurements of fat pads soft-tissue x-rays, and skinfolds, as well as changes in body weights. Some comparisons were made with data obtained by the authors in earlier published experiments on subjects in whom straight uninterrupted reduction methods were employed.

All five subjects on restricted caloric intakes showed calcium deficits by the eighth week. Some of the subjects lost nitrogen and to a lesser extent phosphorus. Control subjects on maintenance diets showed no nutrient losses.

As measured by nutrient deficits, there appeared to be no physiologic advantage in the stepwise reducing regimen over straight reduction. From a psychological standpoint the majority of subjects preferred stepwise reduction to an uninterrupted regimen. It was not possible to evaluate objectively a relation between emotional stability and nutrient losses, although the authors had the impression that those who showed the greatest tendency toward instability were the ones who were losing calcium. FRANK E. RICE

Diet and Weight-Reduction in the Obese. T. R. E. Pilkington, H. Gainsborough, V. M. Rosenoer and M. Carey. *Lancet*, 1: 856, 1960.

The remarkable findings reported by Kekwick and Pawan in 1953 and 1956, to the effect that during short periods on isocaloric submaintenance diets weight loss was greater on a high-fat than a high carbohydrate diet, have been widely applied. These authors consider the previous conclusions unjustifiable in view of the short periods of observation, and report here the effects on weight loss in obese subjects on 800 and 1,000 calorie diets of high fat, high-carbohydrate and mixed composition. The diets were continued for twenty-four-day periods and the general slope of weight loss is convincingly shown to be unaltered by the composition of the diet. When the diets were changed the slope changed temporarily, falling more steeply when a high-carbohydrate diet was replaced by a high-fat diet and often rising when a high-carbohydrate diet was substituted for a high-fat diet. These temporary effects lasted not more than ten days and were probably due to differences of hydration. F. E. HYTTEN

An Evaluation of the Effectiveness of Diet Instruction for the Obese. R. E. Franklin and E. H. Rynearson. *Proc. Staff Meet. Mayo Clin.*, 35: 123, 1960.

A comparison was made of the results of both individualized and group dietary instruction for weight reduction among outpatients at the Mayo Clinic. Patients receiving reduction-diet instruction in a class lose nearly as much weight as do those receiving individual instruction, and the difference is not significant. The authors recommend that either method may be used, and from the point of view of efficiency and time, class instruction may be preferable. S. O. WAIFE

Hypnosis, Diet and Weight Reduction. L. B. Winkelstein. *New York State J. Med.*, 59: 1751, 1959.

The author attempted to evaluate hypnosis as a means of diet control and reorientation of eating habits. An attempt was made to determine whether or not ideas relating to the control of diet could be more deeply implanted in the hypnotic state than under normal circumstances. Forty-two women were selected on the basis of the ability to enter a sufficiently deep trance state and who were in good physical health except for obesity. At the onset the term hypnosis was not used and substitution phrases such as "relaxation and suggestion," "subconscious suggestion" were employed. After several inductions of a deep trance, the suggestions offered would last for several days. Training by hypnotic suggestion was most satisfactory when sessions were held approximately twice weekly for the first two weeks and then once weekly for longer periods of time.

Best results were obtained when suggestions were channeled along such lines as fortification of the desire for weight loss, explanation of caloric bounds, development of proper eating habits including elimination of

between-meal feedings and suggestions as to hunger sensations. The six-months average weight loss for the entire group was about 27 pounds, and patients varied from 9 to 58 pounds in the amount lost. No anorexic or metabolic stimulating drugs were used.

S. O. WAIFE

A Comparative Study of Phenmetrazine and Dextroamphetamine in a Short-Term Reducing Program in Medical Students. M. Patterson. *Antibiotic Med. & Clin. Therap.*, 6: 207, 1959.

Seventy-one medical students, average age twenty-four years, participated in a double-blind test in which phenmetrazine (Preludin®) and dextroamphetamine were used. Only five were grossly obese. The students were placed on a reduced caloric intake and were asked to record their own weights, symptoms and degree of diet-following.

Fourteen students did not complete the course. Forty-five students received phenmetrazine for 281-patient weeks. The average weight loss was 3.32 pounds per week. Twelve students received dextroamphetamine for a total of 92-patient weeks and had an average weight loss of 2.3 pounds per week. According to the author, phenmetrazine was more effective in a short-term reducing program.

Side effects were rather frequent, including insomnia, nervousness, palpitations and headache. However it was not necessary to stop treatment because of the reactions.

S. O. WAIFE

Comparative Effectiveness of Phenylpropanolamine and Dextro Amphetamine on Weight Reduction. J. F. Fazekas, W. R. Ehrmantraut, K. D. Campbell and M. C. Negron. *J.A.M.A.*, 170: 1018, 1959.

A comparative study of the anorexigenic properties of two drugs, phenylpropanolamine and dextroamphetamine, was performed on eighty-one obese but mentally-deficient subjects. These patients were selected to obviate as much as possible the psychologic factors that may influence weight reduction in a "mentally alert population." Food intake was not restricted and the caloric consumption was at least 3,000 calories per day. The study was conducted on a "blind" procedure in that none of the personnel associated with the project were aware of the nature or identity of the drugs administered. The subjects were divided into four groups and each was given one of four preparations three times a day, one hour before meals, for six weeks. At the end of the study it was disclosed that one group received 25 mg. of phenylpropanolamine, the other 50 mg. A third group received 5 mg. of dextroamphetamine, and a fourth group received a placebo.

The results failed to demonstrate a significant reduction in weight in the groups receiving phenylpropanolamine three times a day and in those receiving a placebo. A statistically significant reduction of weight, however, was found in the group receiving 5 mg. of dextroamphetamine three times a day. It should be pointed out that the mean value of weight loss was only 4.6 pounds over a six-week period on dextroamphetamine. There was wide variation in the response of this drug, in that several patients lost 10 pounds, two actually gained weight. The authors conclude that although phenylpropanolamine is chemically related to dextroamphetamine, it does not possess significant anorexigenic properties.

It should be noted that in this study different drugs are compared in different populations. On the other hand, this would probably not alter the outcome of a study of this type.

S. O. WAIFE

Results of Addition of Liothyronine to a Weight-Reducing Regimen. E. P. Gelvin, S. Kenigsberg and L. J. Boyd. *J.A.M.A.*, 170: 1507, 1959.

A double-blind study was planned to compare the efficacy of a capsule containing D-amphetamine and amobarbital with a combination of this capsule and liothyronine (L-triiodothyronine) in the management of obesity among fifty-seven outpatients. The group averaged forty-three years of age and an average weight of 193 pounds. A 1,000-calorie diet was prescribed for all patients (75 gm. protein, 100 gm. carbohydrate, 40 gm. fat). Half the patients received the amphetamine-amobarbital capsule first, the other half received this combination plus liothyronine. After eight weeks the dosage schedules were reversed. Patients were seen at two-week intervals.

The two therapeutic regimens produced equal weight changes for the first eight weeks. More weight was lost by the group that received the amphetamine-amobarbital preparation first and then the addition of liothyronine. At the dosage level used, no effect on the blood pressure, pulse rate or serum cholesterol level was noted. There were no symptoms of "hypermetabolism."

Experiments on weight loss among clinic patients is one of the most difficult of human experiments. All results, unfortunately, must be considered with caution.

S. O. WAIFE

Obesity in Childhood. A Clinical Trial of Phenmetrazine. J. Rendle-Short. *Brit. M. J.*, 1: 703, 1960.

Twenty-one children, who all weighed over the nintieth percentile of weight for age, took part in an investigation. For two weeks they were given no treatment and gained from 1/2 to 5 pounds. For the next four weeks they were given at random either phenmetrazine (Preludin®) tablets or dummy (placebo) tablets and for the next four weeks the opposite to their first tablets. There was no dietary restriction.

On the drug, eighteen of the children lost between 1/2 and 8 pounds, two remained stationary and one gained 4 pounds. On the dummy tablets all the children gained more than on phenmetrazine; seventeen

gained from 1 to 5 pounds, two remained stationary and two lost from 1 to 1½ pounds.

There were no untoward effects except in one child who became ill-tempered while on this regimen, but four weeks, in a condition such as obesity, is hardly a fair trial of possible ill-effects. F. E. HYTTEN

Rapid losses of body water may promote a prompt reduction in body weight. The psychological effect of this change may be used to advantage early in the course of weight reduction programs by employing oral diuretic agents.

Water and Electrolyte Exchanges of Obese Patients on a Reducing Regimen. R. Passmore, J. A. Strong and F. J. Ritchie. *Brit. J. Nutrition*, 13: 17, 1959.

A significant part of the initial weight loss incurred when obese patients go on a reducing diet has been ascribed to loss of body fluids. In this paper a quantitative assessment of the initial water loss and subsequent retention by seven patients is described. Each patient was studied for six weeks on a strictly controlled and rigorous reducing regimen. Under the conditions of the experiment the following observations were made.

Changes in water intake appear to be unrelated to rates of loss of water, and the fluctuation in the urinary output is explained by an inconstant proportion of changes in body water. The loss of fluids by evaporation was quite variable from patient to patient.

Losses and gains of body water were not associated with changes in fluid intake. They could only be partly explained by variations in output. The electrolyte changes indicate that during initial dehydration there were losses of both intracellular and extracellular water. In subsequent periods, water retention was associated with increases of extracellular water despite probable continuing losses of intracellular water. S. O. WAIFE

The Composition of Tissue Lost Through Reduction of Diet in Obese Patients. H. Ljunggren, D. Ikkos and R. Luft. *Brit. J. Nutrition*, 13: 485, 1959.

An estimation of body water and electrolytes was made in seven obese patients who were losing weight. The average composition of the tissue lost was found to contain 14.5 per cent total water (4.4 per cent extracellular and 10.1 per cent intracellular) and 22.7 mEq. of potassium per kg. S. O. WAIFE

In obesity, the metabolizing tissues may be more efficient in the oxidation of fatty acids due to the conditioning of cellular enzymatic mechanisms for these substrates. The obese patient is less likely to utilize carbohydrate efficiently because of this enzymatic setting for fat combustion. The converse is true for non-obese patients who utilize carbohydrate more efficiently than fat.

Resistance to Ketosis in Obese Subjects. A. Kekwick, G. L. S. Pawan and T. M. Chalmers. *Lancet.*, 2: 1157, 1959.

It is well known that ketosis does not develop readily in obese persons. Two possible explanations for this were investigated: (1) that ketone bodies are utilized or excreted faster in obese subjects than non-obese subjects; (2) that ketone bodies do not form so rapidly in obese subjects.

The first possibility was tested by intravenous injections of 30 or 60 mg. per kg. body weight of sodium, β-hydroxybutyrate. Blood levels fell rather more steeply after this injection in obese subjects but the difference was thought to be negligible. Less than 1 per cent of the injected "ketone" was excreted in the urine of either group. The first possible explanation was therefore untenable. To test the second possibility an attempt to produce ketosis was made by feeding obese and non-obese subjects a diet providing 1,000 calories daily of which 90 per cent was supplied as fat. All the obese subjects were able to take the diet for as long as required; the non-obese subjects rapidly became ketotic and seven of eight had to abandon the diet by the fifth day because of symptoms. Progressively lower fasting blood sugar levels developed in the non-obese subjects who were in negative nitrogen balance averaging −8.6 gm. daily. The obese subjects maintained their blood sugar levels and were almost in nitrogen balance.

It is calculated that in neither group was there sufficient carbohydrate available either from the diet or nitrogenous sources to supply even the minimal requirements of the brain and that this suggests the ability, particularly in obese subjects, to produce carbohydrate from fat. F. E. HYTTEN

X. Endogenous Dilution of Administered Labeled Acetate During Lipogenesis and Cholesterogenesis in Two Types of Obese Mice. C. Zomzely and J. Mayer. *Am. J. Physiol.*, 196: 956, 1959.

Determination of dilution of administered labeled acetate by endogenously produced acetate in two types of obese mice, goldthioglucose obese mice (regulatory obesity) and obese hyperglycemic mice (metabolic obesity), shows that this dilution is of the same order for obese and non-obese mice when fed "ad libitum." When fasted, dilution is again of the same order for goldthioglucose obese mice and normal control animals, but is twice as great for obese hyperglycemic mice. These data in conjunction with results obtained on incorporation of C^{14} into fatty acids and cholesterol show that the increased synthesis of these lipids is related solely to the hyperphagia in the case of the goldthioglucose obese mice. By contrast, the obese hyperglycemic mice show rates of fatty acid and cholesterol synthesis which are three times the control levels even when fasted. These results justify the previously drawn distinction between "regulatory" and "metabolic" obesities. AUTHORS

NUTRITIVE VALUE OF MILK

Milk is the oldest food known to man; it receives no less than forty-four references in the Old Testament. Both human and cow's milk supply basic caloric and protein requirements in infant feeding, and the latter provides an excellent nutritional source for adults. Interesting data concerning hypogenesis in a lactating patient indicates that in addition to forming fats de novo *the mammary gland may secrete fats resembling those found in human depot fat.*

The Fatty Acids of Human Milk. II. Alterations Produced by Manipulation of Caloric Balance and Exchange of Dietary Fats. W. Insull, Jr., J. Hirsch, T. James and E. H. Ahrens, Jr. *J. Clin. Invest.*, 38: 443, 1959.

A twenty-three year old white woman was admitted to the hospital on the fifth postpartum day; she remained under metabolic ward conditions for seven weeks on a liquid formula. The breast milk output was determined by weighing the baby immediately before and after each nursing. At the end of a dietary period, milk was collected and sampled.

Lactation was established by the ninth postpartum day, and the daily milk production averaged 723 gm. It was found that the fatty acid composition of human breast milk could be radically altered without affecting the volume or the fat output in the milk. During energy equilibrium, milk fat closely resembled dietary fat. However, when insufficient calories were fed, the milk fat approached the composition of human depot fat. These findings indicate that dietary fatty acids are readily transported into milk fat, but that when the depot fat has to be used for energy the fatty acid excretion in the milk parallels that of its source. When excess calories (nonfat) were fed, the milk showed a striking increase in lauric and myristic acids and a marked decline of all polyenoic acids. Synthesis of fatty acids in the breast appears to be promoted when excess calories are fed, and the accumulation of C_{12} and C_{14} acids in the milk suggest that mammary fatty acid synthesis differs in several important respects from extramammary depots. S. O. WAIFE

The following investigation demonstrates that the fat content of milk can be lowered by manipulation of rations. This will not be a popular study among dairymen.

Production of Low-Fat Milk. I. Effect of Quality and Quantity of Concentrate on the Volatile Fatty Acids of the Rumen and on the Composition of the Milk. J. C. Shaw, R. R. Robinson, M. E. Senger, S. Lakshmanan and T. R. Lewis. *J. Nutrition*, 69: 235, 1959.

The principal objective of this study was to develop rations that would consistently effect a decrease in the fat content of milk. Other workers had shown that the fat content of milk can be depressed by feeding low roughage rations, and that this depressive effect is associated with lowered production of acetate in the rumen and increased production of propionate. Four breeds of cows were used. Various concentrate mixtures were prepared from bread, potato meal, cooked polished rice, corn meal and other cereals, brewers grains, bran, dry skim milk, and varying proportions of alfalfa hay. White bread was used in some feeding studies because of earlier field observations implicating bread in connection with low-fat milk. Rumen fluid was obtained for analysis at intervals about five hours after feeding. Four diets were tested: (1) high protein concentrate plus 4 pounds alfalfa hay daily; (2) white bread, with molasses plus 6 to 7 pounds of hay; (3) low protein concentrate plus 4 pounds hay; (4) low protein plus 12 pounds of alfalfa.

Diet 2 causes a significant reduction in the per cent of fat in the milk as compared with the other three diets, among which no differences were apparent. During the feeding period total milk production decreased in all groups; group 3 showed the greatest reduction, group 1, the least. Analyses of rumen samples showed highest acetic acid in group 4, lowest in group 2; in propionic acid, highest in group 2. The reduction in rumen acetate seems to be implicated in lowering the percentage of fat in the milk. (It is noted that acetate has been demonstrated to be a precursor of the lower fatty acids.) Milk solids, nonfat, remain relatively constant regardless of diet. FRANK E. RICE

Vegetable oils substituted for butterfat in the diet of calves produces a number of undesirable effects.

Some Effects of Feeding Various Filled Milks to Dairy Calves. I. Physical Condition and Weight Gains, with Special Reference to Low-Fat Rations. R. S. Adams, T. W. Gullickson, J. E. Gander and J. H. Sautter. *J. Dairy Sc.*, 42: 1552, 1959.

Previous studies have established that highly unsaturated vegetable oils adversely affect growth and physical conditions when used as substitutes for butterfat in the diet of dairy calves. In the present experiments, filled milks were prepared by homogenizing the various test fats at a 3.5 per cent level into pasteurized skim milk, which in some cases had been fortified with nonfat milk solids. Minerals and vitamins were added as required. Observations were made on 150 calves.

When corn oil-filled milks were fed, there resulted marked diarrhea, various symptoms of unthriftiness including susceptibility to infections, muscular involvement and early death. These observations were in marked contrast to the results from feeding whole milk, or filled milks compounded from hydrogenated corn oil, hydrogenated cottonseed oil, lard, or blends of hydrogenated cottonseed oil and soybean oil, or a butter oil-filled milk. The presence of 0.1 to 0.15 per cent butterfat in the fortified skim milk ration was sufficient to produce normal growth and physical conditions in calves from fourteen days up to ninety days of age. (Note that during the first fourteen days of life the calves had been receiving colostrum and whole milk.) The daily

growth rate of animals on a filled milk prepared from fortified skim milk and the mixture of hydrogenated cottonseed oil and soybean oil was unusually high, even greater than the growth rate of the animals on whole milk or fortified skim milk. Supplementation of the corn oil diets with high levels of tocopherol prevented the development of muscular involvement but did not improve weight gains. It is concluded that "the inclusion of corn oil in the diet depresses growth in some manner." FRANK E. RICE

Some Effects of Feeding Various Filled Milks to Dairy Calves. II. Fecal Characteristics and Digestibility Data. R. S. Adams, J. E. Gander, T. W. Gullickson and J. H. Sautter. *J. Dairy Sc.*, 42: 1562, 1959.

"Filled milks" prepared by homogenizing various fats at the 3.5 per cent level into skim milk were fed to calves. Corn oil-filled milks induced severe diarrhea, which was not reduced by dietary supplementation with tocopherol. Dry matter digestibility coefficients for the corn oil-filled milks were lowest of all. There were no significant differences between the others, hydrogenated corn oil, butter oil or lard.

Feces of animals fed skim milk with no more than 0.1 per cent fat contained 5.36 per cent fat on the dry matter basis. This figure, assumed to be metabolic fecal fat, was deducted from the total fat excretion in calculating fat digestibility. Fat digestibility data show that butter oil is superior to that of the other fats.

Studies of fecal fats showed about the same partition between neutral fat, soaps and free fatty acids, whether the animals were on a fat-free diet or one containing butter oil. The partition pattern on feeding any of the other fats was significantly different. The fecal fat from the fat-free and butter oil diets analyzed higher in neutral fat and lower in soaps than when any of the other filled milks were fed. FRANK E. RICE

Some Effects of Feeding Various Filled Milks to Dairy Calves. III. Blood Plasma Tocopherol and Vitamin A. Levels, Diet Storage Effects, and Evidence of Toxicity. R. S. Adams, J. E. Gander, T. W. Gullickson and J. H. Sautter. *J. Dairy Sc.*, 42: 1569, 1959.

The continued feeding of corn oil-filled milk to calves resulted in lowered blood plasma levels in both tocopherol and vitamin A. Lowered blood tocopherol levels also were observed when feeding lard-filled milk, or a ration containing butter oil which had been prepared from oxidized butter. Plasma tocopherol levels could be raised by supplementing the corn oil and lard diets with tocopherol. Storage of corn oil-filled milks caused rapid reduction in tocopherol content; in one sample 42 per cent was lost in seven days. The feeding of such samples to young calves had a detrimental effect, possibly due to the presence of peroxides formed during storage. FRANK E. RICE

Reviews of the Progress of Dairy Science. Section D. Nutritive Value of Milk and Milk Products. W. A. McGillivray and J. W. G. Porter. *J. Dairy Res.*, 25: 344, 1958.

This is a review of the literature from January 1956 to January 1958, mainly on milk fat, milk protein, vitamins and milk in infant nutrition and includes 263 references.

A preponderance of evidence suggests that there is no significant difference between the nutritional values of raw, pasteurized and sterilized milk, although one investigator reported greater weight gains in feeding raw milk to rats. In infant nutrition, the authors draw the following conclusion from their review of th extensive literature: "In general, recent work would seem to support the previous conclusions that a number of artificial milks are, for all practical purposes, in no way nutritionally inferior to human milk . . ." ". . . the conflicting results being attributable largely to the different techniques employed, some methods not necessarily measuring nutritive value and others being susceptible to factors entirely unrelated to the diets fed." Special attention is given to the literature on the effect of sterilization by heat, and by radiation, on the biological value of milk proteins and on the availability of the lysine.

Publications are reviewed wherein milk fat has been compared with other fats from the points of view of digestibility, absorption rate, growth action, degree of saturation of the fatty acids, blood cholesterol levels related to diet and such. The authors find it difficult to speculate on the significance of some of the findings. A dietary interrelationship between milk fat and milk carbohydrate (lactose) has been demonstrated to be more favorable than when corn oil and lactose are fed together. FRANK E. RICE

An optimum level of dietary fat for the production of enzymes by lactating women has been demonstrated. This may be related to the caloric requirements for synthesis of these protein factors.

Relation Between Dietary Fat, Fat Content of Milk and Concentration of Certain Enzymes in Human Milk. M. G. Karmarkar and C. V. Ramakrishnan. *J. Nutrition*, 69: 274, 1959.

Sixty lactating women in normal health living in and around Baroda, India, and in about the same lactation period (three to four months), were the subjects of this study. Milk samples were collected uniformly at about 3 P.M. Dietary fat intake averaged 60.54 gm. per day as compared with groups receiving 37.43 and 18.36 gm. per day. The milk produced was significantly higher in fat, and in lipase, esterase and alkaline phosphatase activity. Milk produced by mothers' with a fat intake averaging 88.98 gm. per day was no higher in fat content, nor was the lipase, esterase or alkaline phosphatase activity significantly higher. Acid phosphatase declined steadily with increasing fat intake. It

was observed that neither dietary protein nor milk protein affected the activities of these enzymes.

FRANK E. RICE

The importance of trace elements in human nutrition is now widely appreciated. Further studies of these factors, as they exist in milk, as one of the most widely used foods are essential.

Trace Elements in Milk. A Review. Parts I and II. J. G. Archibald. *Dairy Sc. Abstr.*, 20: 711, 799, 1958.

At least two factors have tended to turn attention to trace elements in recent years: (1) discovery of the importance they play in metabolism as constituents of body pigments, enzymes and hormones, important especially to the young of all species; and (2) constant refinement of methods of analysis. This is a critical review, with 194 references, of our present knowledge with respect to aluminum, arsenic, barium, boron, bromine, manganese, molybdenum, nickel, radium, rubidium, selenium, silicon, silver, strontium, tin, titanium, vanadium and zinc.

Data on human milk are reported, and the milk of other species, as well as the cow. Figures are given on variations between colostrum and milk, and on the effect of supplementing the feeds with salts of the trace elements.

References to the iron content of milk outnumber those pertaining to any other element. While iron is present normally in the cow's milk as drawn (average 0.45 p.p.m.), more is found in milk which has passed through a processing plant. At best cow's milk must be considered a poor dietary source of iron. Human milk generally is found to run only a little higher (average 0.8 p.p.m.). More zinc has been found in milk than any of the other trace elements. Human milk averages 4.4 p.p.m., normal cow's milk 3.7 p.p.m. Milk that has been in contact with galvanized surfaces may run very high in zinc. Cobalt is present in the milk of ruminants when it is in the ration. Microbiological conversion to vitamin B_{12} takes place in the digestive canal of these animals. Copper is normally in cow's milk, the average being 0.13 p.p.m. Human milk averages 0.5 p.p.m. In commercial processing, the milk picks up additional copper from plant equipment and containers. Cow's milk averages 0.15 p.p.m. of fluorine. The amount in the milk can be raised significantly by giving the cow large doses of fluorine either in feed or drinking water. This has been suggested as a means of bringing this important element into the diet of those in whom it would do the most good and more readily than through the water supply. Iodine in cow's milk averages 0.04 p.p.m., somewhat more in milk produced in coastal areas than in central areas.

Manganese is present normally in cow's milk, average 0.03 p.p.m. One investigator reports 100 to 150 p.p.m. of manganese in the ash of human milk. Molybdenum is normally in milk as well as blood, bile and eggs. The element has been found to be associated with the enzyme, xanthine oxidase.

The authors conclude that the values reported in the literature of trace elements other than those recorded herein, are too scanty and variable to justify averaging. Except for copper and iron, the effect of feeding supplements of each specific element increases the amount of that element in the milk. Response to feeding the other elements varies from slight to very marked. Colostrum of all species contains more of any trace element than is found in the "normal" milk.

Differences of opinion prevail as to the form in which the trace elements exist in milk. It is generally agreed that they are linked in organic complexes, perhaps "chelated." There is evidence that iron and copper are protein-bound and that the protein-metal complexes are adsorbed on the surface of the fat globules.

FRANK E. RICE

Distribution of Natural and Added Copper and Iron in Milk. R. L. King, J. R. Luick, I. I. Litman, W. G. Jennings and W. L. Dunkley. *J. Dairy Sc.*, 42: 780, 1959.

Earlier studies have occasionally indicated that copper and iron naturally occurring in milk is predominantly a part of the protein that surrounds the fat globules, i.e., in the cream of the milk, whereas copper and iron that have their origin from direct addition, may be expected to be found in the skim milk fraction. The present investigators undertook to obtain evidence on these points using modern radioactive-tracer technics. Radioactive copper and iron were (1) infused into the jugular vein of cattle ("natural" copper and iron in the milk results from this treatment) and (2) added to the warm milk immediately after being drawn. The milk was then centrifuged; both the skim milk and cream were further fractionated.

Natural copper favored the fat phase of the milk. From 10 to 35 per cent was found to be associated with the washed fat globules. The membrane surrounding the fat globules contained fifty times as much natural copper per 1 per cent of protein as in the casein and whey proteins. Natural iron also was highly concentrated at the fat globule surface. On the other hand, of the added copper only 2 to 3 per cent appeared in the fat globule membrane, and none of the added iron.

The findings have some significance in comparing the nutritional value of whole milk and skim milk, the former having the advantage in retaining more of the copper and iron found naturally in milk.

FRANK E. RICE

GLUCOSE, FAT AND THE LIVER

The release of glucose from hepatic stores of glycogen in response to hypoglycemia is one of the important mechanisms in the maintenance of normal blood glucose levels. Experimental preparations have indicated the probability of an increased secretion of glucagon and/or epinephrine in promoting glycogenolysis under these conditions. However, the continued intraportal infusion of insulin,

either endogenous or exogenous, appears to inhibit glucose-6-phosphatase activity resulting in a reduced rate of glucose release creating hypoglycemic unresponsiveness until insulin effect is terminated.

Effect of an Insulin Infusion on Hepatic Output of Glucose. M. B. Fine and R. H. Williams. *Am. J. Physiol.*, 198: 645, 1960.

Catheters were placed in the hepatic and portal veins of normal dogs and were maintained for varying periods of time. With these animals in an unanesthetized state, and recovered from the acute effects of the catheter implantations, infusions of small amounts of insulin were made slowly into the portal vein and the hepatic output of glucose was determined. It was concluded that, under the experimental conditions, insulin did not significantly depress the hepatic output of glucose but that it did inhibit the hepatic response to hypoglycemia. The hepatic glucose output during the infusion was similar to control values, but there was a marked rise in glucose output following the cessation of the infusion. AUTHORS

Effect of Insulin on Hepatic Blood Flow in the Unanesthetized Dog. W. C. Shoemaker, R. Mahler, J. Ashmore and D. E. Pugh. *Am. J. Physiol.*, 196: 1250, 1959.

The immediate and direct effect of intravenously or intra-arterially administered insulin upon hepatic blood flow was studied in unanesthetized dogs whose hepatic vessels had been previously catheterized. Comparison was made between two dose levels, 0.1 or 0.2 unit/kg. and 1 unit/kg., the latter being infused over a thirty-minute period. At the 0.1 or 0.2 unit/kg. range, there was no immediate statistically significant increase in flow. Sporadic increases in flow occurred in about half the animals during the recovery phase of the hypoglycemia (twenty to forty-five minutes after the administration of insulin). At the 1 unit/kg. level, insulin produced a definite increase in hepatic blood flow which reached its maximum at fifteen minutes. These changes in flow were interpreted as secondary effects to the insulin-induced hypoglycemia. AUTHORS

Effects of Glucagon and Tolbutamide on Glycogen in Isolated Perfused Rat Liver. L. L. Miller, J. E. Sokal and E. J. Sarcione. *Am. J. Physiol.*, 197: 286, 1959.

The glycogen content of the isolated perfused liver taken from fed normal rats is remarkably stable for three to six hours (*Am. J. Physiol.*, 195: 295, 1958) and thus affords an isolated system for studies of the effect of various agents on glycogen synthesis and glycogenolysis. The effects of glucagon and tolbutamide in this system are described. Glucagon given by continuous infusion (30 to 225 μg./hour) caused prompt glycogenolysis, with blood glucose concentrations rising to levels as high as 970 mg. per cent. Hyperglycemia of 600 to 700 mg. per cent did not inhibit the glycogenolytic action of glucagon; however, at glucose levels of 800 to 1,000 mg. per cent glycogenolysis did not proceed to completion. High concentrations of tolbutamide, maintained before and during the administration of glucagon, failed to inhibit the glycogenolytic action of the latter agent. AUTHORS

Does a Glucose Load Inhibit Hepatic Sugar Output? C^{14} Glucose Studies in Eviscerated Dogs. R. Steele, J. S. Bishop and R. Levine. *Am. J. Physiol.*, 197: 60, 1959.

A sequence of changes in plasma glucose specific activity is observed in intact dogs when a large amount of C^{12}-glucose is injected intravenously following the tagging of the circulating glucose by an injection of a minute amount of C^{14}-glucose. Similar changes are observed when the same procedure is applied to eviscerated dogs in which the plasma glucose concentration is being maintained by a continuous infusion of C^{12}-glucose, this infusion being continued unchanged after the C^{12}-glucose load is given. These results show that inhibition of hepatic glucose output is not the only or the necessary explanation for the cessation in the exponential fall of plasma glucose specific activity which is seen in the intact dog following an intravenous load of C^{12}-glucose. An alternative explanation of the effect is offered which is based on the slowness of mixing of the injected C^{12}-glucose load with a part of the body glucose pool. AUTHORS

The production of fatty acids and cholesterol by liver tissue requires hydrogen ions derived from reduced triphosphopyridine nucleotide (TPNH). The principal source of TPNH is provided by the oxidative pathway of glycolysis. Animals maintained on high fat diets manifest low rates of lipogenesis as glucose utilization is reduced.

Influence of Diet on Utilization of Glucose and Incorporation of Acetate-1-C^{14} into Liver Fatty Acids and Cholesterol in Rats. J. Christophe and J. Mayer. *Am. J. Physiol.*, 197: 55, 1959.

A comparative study of glucose utilization, insulin sensitivity and *in vivo* incorporation of acetate-C^{14} into liver fatty acids and cholesterol was conducted in male adult rats. These animals were maintained for four weeks on three high carbohydrate diets (glucose, fructose or galactose), a high protein diet (casein), a high fat diet (lard) or Ralston Purina laboratory chow. Glucose utilization was high in rats on the glucose diet and low in those on the fat diet. Incorporation of C^{14} into liver fatty acids was very high in rats on the fructose diet, high in rats on the protein and glucose diets, low in rats on chow, and very low in rats on the fat diet. Incorporation of C^{14} into liver cholesterol was relatively high in rats on chow and relatively low in those on the fat diet. Glucose utilization in prefasted states and in-

corporation of acetate into liver fatty acids in fed states were roughly parallel in rats on various diets, but no correlation could be noted between glucose utilization and acetate incorporation into liver fatty acids on the one hand and incorporation of acetate into liver cholesterol on the other. AUTHORS

Effects of Cold Acclimation on Hepatic Carbohydrate and Lipid Metabolism. J. M. Felts and E. J. Masoro. *Am. J. Physiol.*, 197: 34, 1959.

The acclimation of rats to low environmental temperatures was found to alter the hepatic metabolic response to fasting for one day at 0 to 2°C. Liver glycogen was stabilized, fatty infiltration of the liver did not occur and liver slices were better able to oxidize acetate-1-C^{14} and palmitate-1-C^{14} to $C^{14}O_2$. These results provide an excellent example of an acclimation process occurring at the molecular level. AUTHORS

Relationship Between Choline-Deficient Fatty Liver and Chronic Alloxan Diabetes in Rats. A. M. Cohen. *Am. J. Physiol.*, 198: 637, 1960.

Choline deficiency in chronic alloxan-diabetic rats resulted in deterioration of the diabetic state. In alloxan-diabetic rats fed a choline-deficient diet the fatty infiltration of the liver was less than in nondiabetic rats on the same diet. Insulin administered to alloxan-diabetic and nondiabetic, choline-deficient rats further decreased the hepatic fat content and improved the diabetic state in the former. Administration of insulin during life caused a marked increase of fatty acid synthesis in liver slices from both choline-fed and choline-deficient, alloxan-diabetic rats. Substituting fructose for starch in the choline-deficient diet failed to increase the hepatic fat of the diabetic or the nondiabetic animals. The decrease in hepatic fat following the administration of insulin to choline-deficient, alloxan-diabetic rats is apparently due to an extrahepatic effect of insulin, for it occurs despite the increased synthesis of fat in the liver induced by insulin. AUTHOR

Deposition of fat within the livers of obese subjects and of polyphagic experimental animals has been demonstrated. The well known lipotropic effects of choline and casein do not prevent lipid infiltration associated with obesity.

Hepatic Lipid Produced by Polyphagia in Albino Rats. Relationships to Dietary Choline and Casein. J. S. Meyer and W. S. Hartroft. *Am. J. Path.*, 36: 365, 1960.

In young male Albino rats polyphagia and obesity were produced by electrocoagulation of the ventromedial nuclei of the hypothalamus with the aid of a stereotaxic instrument. In the first experimental group (rats weighing 117 to 148 gm.), the effect of dietary choline was studied in thirty-nine rats operated upon and fourteen rats not operated upon which were fed a semisynthetic diet supplemented with 0.05 or 0.5 per cent choline chloride, respectively, for about two months. In the second experimental group (rats weighing 155 to 275 gm.), the additional effect of increased amounts of casein was tested in forty-nine rats operated upon and ten not operated upon which were fed a stock diet or a diet containing 20 per cent casein, respectively, with a supplement of 0.5 per cent choline. Only the rats that were operated upon became polyphagic and about 50 per cent were obese.

At necropsy, hepatic lipid content (wet weight) and total lipid concentration of the carcasses were determined and the distribution of fat in the liver was studied with the light and the electron microscope. Obesity was associated with hypertrophy and fatty change of liver cells. The fat consistently accumulated in the periportal areas of the liver lobules in the form of droplets in cytoplasm and nuclei, while the cells retained their polygonal shape. The amount of fat sometimes was as much as 47 per cent of the wet weight of the liver. The microglobules of fat failed to coalesce or to be extruded to form fatty cysts as seen in choline-deficient rats. The liver cells of polyphagic rats were thus capable of storing large amounts of fat without cell injury as occurring in choline deficiency. The lobular distribution of fat differed also from that in choline deficiency inasmuch as in the polyphagic rats fat was deposited first in portal areas rather than pericentrally, and cells about the central vein remained to some degree unaffected even in the presence of advanced fatty metamorphosis. Neither a high concentration of choline nor the supplement of casein decreased the fatty change or altered its pattern of deposition in the liver cells.

The observations indicate that high caloric intake did not increase the choline requirements in young rats, and that progressive accumulation of periportal lipid could be prevented by choline or casein supplements.

M. SILBERBERG

Protection against hepatic lipid infiltration and hemorrhagic renal changes induced by choline deficiency is provided by the administration of linoleic acid and by diethylstilbesterol. The effect of these substances upon choline metabolism requires further investigation.

Incorporation of Exogenous Choline into Liver and Biliary Phospholipids. F. Nakayama and C. G. Johnston. *Am. J. Physiol.*, 197: 327, 1959.

Since choline is an essential part of biliary phospholipid, which has a definite effect on holding cholesterol in solution in bile, the incorporation of exogenous choline into liver and biliary phospholipid has been studied using choline-methyl-C^{14} and silicic acid column chromatography. Exogenous choline is demonstrated to be rapidly incorporated into liver lecithin, sphingomyelin and biliary lecithin. Indirect evidence is presented showing that bacterial degradation of choline in the intestine is not likely responsible for the urinary excretion of large amounts of trimethylamine after the oral

administration of choline. The choline portion of ingested lecithin is metabolized similar to free choline: ingested lecithin, which is absorbed as such from the intestine, will remain in general circulation for a considerable length of time. AUTHORS

A Substance in Liver Which Inhibits Thymine Biosynthesis by Bone Marrow. J. S. Dinning and L. Wiles. *Science*, 129: 336, 1959.

Duplication of deoxyribonucleic acid (DNA) must occur in the cycle of cell division. In certain tissues there must exist some mechanism for the control of the mitotic rate. It, therefore, seemed possible that there might exist in tissues naturally occurring inhibitors of DNA biosynthesis which then would be mitosis inhibitors. Rabbit bone marrow homogenates or cell suspensions were incubated with sodium formate-C^{14}, and the incorporation of the formate into RNA and DNA was measured. It was found under the conditions described that bone marrow homogenates actively incorporated formate into DNA, whereas liver homogenates did not. Further, when liver homogenates were added to the bone marrow system, there was marked inhibition of DNA biosynthesis. Some attempts were made to concentrate this liver factor. The material is alcohol-soluble. Further studies indicated that this inhibition is due to thymine biosynthesis inhibition.

This work has obvious fundamental importance, and it is hoped that further work along these lines will continue. S. O. WAIFE

Effect of Hepatic Dysfunction on Circulating Levels of Sulfobromophthalein and Its Metabolites. J. V. Carbone, G. M. Grodsky and V. Hjelte. *J. Clin. Invest.*, 38: 1989, 1959.

This study indicates that patients with viral hepatitis and cirrhosis of the liver conjugate BSP (sulfobromophthalein) poorly and retain large amounts of the unconjugated dye. On the other hand, patients whose liver function is impaired as a result of methyltestosterone therapy or extrahepetic biliary obstruction conjugate the dye and accumulate large amounts in the serum. This accumulation may be noted before changes in the serum bilirubin, alkaline phosphatase and glutamic oxalacetic transaminase are evident. Thus, the measurement of the BSP conjugates may differentiate liver defects. S. O. WAIFE

ITEMS OF GENERAL INTEREST

Serum-Albumin Catabolism and Nitrogen Excretion. J. W. L. Davies, C. R. Ricketts and J. P. Bull. *Lancet*, 1: 346, 1959.

It is well known that protein catabolism is increased, for example, after injury, but a quantitative measure of this destruction can only be made by the tedious expedient of nitrogen balance.

In this preliminary communication a simple measure is suggested. An injection of albumin labeled with radioactive iodine is given; when this breaks down the iodine is not recombined in the body with other albumin but is excreted (so long as the thyroid gland is saturated). The breakdown in plasma albumin closely parallels the breakdown of body protein generally so that the estimation of I^{131} excretion is a measure of the body's protein catabolism. Three illustrative cases are given. F. E. HYTTEN

Effect of Potassium and Calcium Deficiency on the Monophasic Action Potential, Electrocardiogram and Contractility of Isolated Rabbit Hearts. B. Surawicz, E. Lepeschkin, H. C. Herrlich and B. F. Hoffman. *Am. J. Physiol.*, 196: 1302, 1959.

Isolated rabbit hearts were perfused with Krebs-Henseleit solution deficient in potassium, calcium or both. Ventricular monophasic action potentials registered with the suction electrode, electrocardiograms and intraventricular pressures, were recorded simultaneously for periods up to twenty minutes. Perfusion with potassium-deficient solutions resulted in a brief initial prolongation of the entire descending limb of the action potential and of the T wave, followed by progressive increase in slope of the initial portion and decrease in slope of the terminal portion of the action potential. During this time the T wave became shorter and a U wave-like deflection occupying the entire diastole developed. QRS showed progressive prolongation. Finally, A-V conduction disturbances, ectopic beats and ventricular fibrillation developed. The force of contraction increased slightly. Perfusion with calcium-deficient solutions decreased the slope of the initial portion while increasing the slope of the terminal portion of the action potential. This was accompanied by prolongation of the S-T segment and reversal in the direction of the T wave. The duration of the action potential reached a maximum after forty to eighty seconds of perfusion, while the force of contraction decreased progressively. Perfusion with solutions without potassium and calcium prolonged the initial as well as terminal portion of the action potential.
AUTHORS

Observations on the Urinary Output of Some B Vitamins in Rats Treated with Tetracycline. F. B. Nicolis and S. Nani. *Acta Vitaminol.*, 13: 97, 1959.

Some observations on the urinary output of B vitamins (pantothenic acid, vitamin PP, vitamin B_{12}, folic acid, thiamine and vitamin B_6) in rats treated with tetracycline 50 mg./kg. for thirty-five days and 200 mg./kg. for twenty days are reported. The results show the great variability in the urinary output of B vitamins following the administration of the antibiotic. An increase of these factors was sometimes observed, which can reach the significance level: sometimes a decrease or even no variation at all was observed.
AUTHORS